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TITLE: COGNITIVE RESERVE AS NEUROPROTECTION FOR COGNITIVE FUNCTIONS IN INDIVIDUALS WITH CLINICAL HYPERTENSION

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COGNITIVE RESERVE AS NEUROPROTECTION FOR COGNITIVE FUNCTIONS IN INDIVIDUALS WITH CLINICAL HYPERTENSION

By

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DISSERTATION

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DEDICATION

To my beloved mother Adele Ipu Amor
To David Drasnin, PhD who both nurtured the scientific thirst in me,
I dedicate this work.

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CHAPTER 1: INTRODUCTION

The construct of reserve with its two components (i.e., cognitive reserve and brain reserve capacity) has been shown by epidemiological and neuroimaging studies to explain differences in clinical outcome between individuals with age-sensitive neuropathology (Stern, 2012, 2009, 2006, 2002). The theory of cognitive reserve (CR) suggests that premorbid and repeated activities, which actively enhance the brain, moderate the clinical expression of pathology among individuals. In the same way, studies of brain reserve capacity (BRC) have indicated that a quantity of neural connections or brain volume passively constitutes a buffer to the brain when the individual's brain is exposed to a brain insult (Lee, 2005). Other researchers have suggested two other models of reserve, which are motivational reserve (MR) and emotional reserve (ER). Motivational reserve consists in sets of motivational and cognitive abilities (e.g., decision regulation, motivation regulation, activation regulation, and self-efficacy) that help individuals to become resilient when experiencing brain damage (Forstmeier and Maercker, 2008). Emotional reserve (ER) researchers have also reported that pre-existing emotional factors (e.g., early attachment, personality traits, and temperament types) build a psychological resilience in individuals which helps in coping with medical and psychiatric conditions (Sela-Kaufman, et al., 2013).

To study the moderation function of reserve between pathology and clinical outcome, researchers have used a constellation of pre-existing and repeated cognitive activities as proxies of reserve. Extant studies have used, separately or collectively, the following variables as proxies of CR: early family environment and genetic factors (Lee, 2005), IQ (Christensen, et al., 2006), education/literacy (Alexander, et al., 1997), occupation (Ropachi,

et al, 2006), leisure activities (Scarmeas, et al., 2003), and social activities (Hultsch, et al, 1999). Some of these social and physical activities use more fluid skills (e.g., solving crossword puzzles, doing art, playing chess, and sewing without a pattern) while other activities require crystalized abilities (e.g., reading a book or a newspaper and writing letters). Fluid skills have been considered to be more "vulnerable" to age-related brain pathology while crystalized activities have been found to remain "resistant" and less sensitive to the aging process (Richards, Sackers, & Deary, 2005). Therefore, participating regularly in fluid activities has been suggested as a protection against aging changes in the brain and nervous system, the cardiovascular system, the respiratory system, and the metabolic and hormonal system (The Mayo Clinic Plan, 2006). To investigate the relation between BRC and brain pathology, researchers have counter the number of synapses and measured cranial capacity (Bigio, et al., 2002), brain volume, head circumference (Mortinez & Snowdown, 1997), and differential metabolism in some sub-regions of the brain (MacLullich, et al, 2002). Researchers have also used some emotional factors such as personality types (e.g., extroversion/introversion, neuroticism, openness, agreeableness, and consciousness), attachment types (e.g., secure, insecure/resistant, avoidant, and disorganized attachment), and temperament (e.g., irritable, fearful, and persistent) to understand the inverse relationship between ER and clinical outcome.

To affirm the relation between CR and the clinical expression of the disease through neuropsychological assessment, researchers have investigated different pathologies. Extensive literature on CR exists in regard to different forms of dementia (e.g., Alzheimer's disease, Parkinson disease, and multiple sclerosis) (Stern, 1995, 1997, & 2002; Mortinez &

Snowdown, 1997; Alexander, et al., 1997), traumatic brain injury ((Sela-Kaufman, et al., 2013; Dennis, et al., 2005), chronic obstructive pulmonary disease (COPD) (Stuss, et al., 1997), and hepatitis C virus (Shipley & Zachary, 1991). In addition, other experts have examined the protective impact of CR against cognitive deficits in individuals with human immunodeficiency virus (HIV) (Stern, et al, 1996), systemic lupus erythematosus (Monasterio et al, 2001), and psychiatric disorders (e.g., schizophrenia, depression, and bipolar disorders). Finally, other studies have assessed the influence of CR in patients with cardiovascular diseases (Lopez, et al., 2003).

An examination of available literature, however, shows that less is known about CR as a moderator between essential hypertension (HTN) and its clinical outcome. However, previous studies using some variables (e.g., literacy, aerobic exercise, spirituality, and education) have reported an inverse association between these variables and the clinical expression of hypertension (Swift, Earnest, Blair, & Church, 2013; Loucks, Abrahamowicz, Xiao, & Lynch, 2011). Consequently, it is imperative to investigate whether or not there is an inverse relation of CR as a moderator between hypertension and silent vascular cognitive impairment. There are four reasons: (1) hypertension affects one third of the world population (WHO, 2012) and 66.7% of US population of adults from 60 years and over (NCHS, 2012); (2) its slow and silent consequences for the brain (e.g., multi-infarcts, stroke, and vascular dementia) and the body (e.g., renal and heart diseases); (3) its late manifestation and insidious progression; (4) and ambiguous findings about the efficiency of antihypertensive medications in protecting cognitive decline. Given the magnitude of hypertension, also called “silent killer” (Kaplan and Victor, 2010), it is important to

understand and study possible factors that could mediate its clinical outcome, especially cognitive reserve (CR).

The purpose of this present project is to investigate whether or not CR protects individuals with clinical hypertension against silent vascular cognitive impairment while controlling for age, medications, and diseases. The findings of this study will contribute to scientific understanding of the reserve construct and will help clinicians target early interventions for individuals with primary hypertension. This study will use different neuropsychological and self-report measures to assess a sample of individuals with essential hypertension without any other advanced dementia or thought disorders. Ethical considerations and legal issues will be taken into consideration in order to protect the rights of participants.

CHAPTER 2: COGNITIVE RESERVE CONSTRUCT

2.1. Terminology

The medical concept of reserve is well-known in the physiology of some organs. For example, renal and liver reserves are well known because of their involvement when the organ suffers a decrease in its capacity to supply to the body. Therefore, the reserve is called up before significant damage to the organ becomes apparent (Sachdev, et al., 2009). It is in this line that Stern (2012, 2009, 2006, 2003, 2002) has formulated the concept of cognitive reserve (CR) after taking into account epidemiological and neuroimaging evidence of patients with Alzheimer's disease. The construct of reserve has been suggested to explain the discrepancies between the degree of neuropathology and its clinical outcomes in patients (Stern, 2009). The reserve construct proposes that individual differences in cognitive processes or neural networks are factors which help some individuals tolerate brain pathology and maintain cognitive function (Stern, 2012). Therefore, Stern (2012, 2009, 2006, 2003, 2002) understands the construct of reserve as a resilience or buffer for the severity of the clinical outcome of a brain pathology after the individual has reached the pathological threshold. Stern (2002) divides the concept of cognitive reserve into two models: passive (i.e, brain reserve capacity) and active (i.e., cognitive reserve).

2.1.1. Brain Reserve Capacity (BRC)

Brain reserve has been defined as individual variabilities in the brain itself which help some individuals to become more resilient than others while dealing with neuropathology (Stern, 2009). In this model, differences among individuals in their reserve have been shown to be dependent on some neurological characteristics (Sachdev & Valenzuela, 2009).

Previous studies have identified the following neurological characteristics as proxies of brain reserve: brain volume, head circumference, neuronal number, synaptic count and density as well as dentritic branching and white matter connections (Stern, 2009; Sachdev et al, 2009).

Some of these proxies of brain reserve have been found to be poor measures. For example, Sachdev and Valenzuela (2009) have reported poor association between head circumference and cognitive function. Some researchers have indicated that metabolic activity of the brain was a better proxy of brain reserve than brain volume or size. For example, a number of studies have found that premorbid brain volume was a proxy of brain reserve (Moro et al., 1997). However, Perneczky and colleagues (2009) have found that metabolic activity of the brain was a better predictor of functional capacity of the brain than brain size (Perneczky et al., 2009). These researchers have noted that glucose hypometabolism in the right temporoparietal cortex was associated with deficits in activities of the daily living.

Brain reserve capacity has been described in a passive, quantitative, and threshold model. As a passive model, Stern (2012) has indicated that there are individual differences in the quantity of available neural substrates that are subjected to a brain insult. The quantitative model takes the concept of reserve as related to neuronal count and dependent on the size of neural substrates (e.g., a larger brain, a greater head size, or the intracranial volume). Furthermore, the threshold model underlines the importance of a fixed cutoff neuronal count after which the manifestation of brain damage becomes apparent through marked cognitive deficits. In addition, the threshold model proposes similarities of effect for various types of brain damage in a person. This model also recognizes differences between individuals in

terms of brain capacity and damage (Stern, 2009). The individual differences have been associated with life experience, which promotes neurogenesis and angiogenesis (i.e., formation of new blood vessel from pre-existing vessels). In addition, life experience is known to contribute to resistance to apoptosis (i.e., the process of cell death) and up-regulating compounds which promote neuroplasticity (Stern, 2012). In summary, brain reserve capacity has been presented as a passive, quantitative, and threshold neurological model which may show some limitations in explaining neuropathology and its clinical manifestations.

2.1.2. Cognitive Reserve

Stern (2012, 2009, 2006, 2003, 2002) has described the construct of "cognitive reserve" (CR) as an active and dynamic behavioral model. Contrary to brain reserve capacity, cognitive reserve does not derive from brain size or neuronal count but from individual differences in cognitive processing and in coping efficiently with neuropathology (Stern, 2002). In several of his review articles, Stern (2012, 2009, 2006) has noted that CR is a model which assumes neither a fixed cut off nor a threshold. Nevertheless, the author has indicated that according to the CR model the individual uses pre-existing cognitive processes or compensatory processes as ways of tolerating a brain lesion. Enriched environment, socio-economic status factors (e.g., occupational and educational attainment or income), leisure activities, and physical activities have been shown to influence CR (Stern, 2012, Valenzuela & Sachdev, 2009; Yaffe, et al., 2009; Tuokko, et al., 2003). In this sense, Stern (2012) has subdivided the CR construct into two components, neural reserve and neural compensation.

Neural reserve has been defined as "inter-individual variability--perhaps in the form of differing efficiency, capacity, or flexibility--in the brain networks or cognitive paradigms that underlie task performance in the healthy brain" (Stern, 2009, p.2016). Studies have found that individuals with more efficient networks had greater capacity, and were more flexible and capable of sustaining brain damage (Stern, 2012). Stern and colleagues (2005) have shown that young individuals use neural reserve when exposed to high task demands. The results of this study indicate that individuals with high CR use greater activation of the brain in efficient ways under highly demanding cognitive tasks. In this sense, Stern (2012) has suggested that high CR provides efficiency, resilience, and a greater capacity to cope with brain pathology.

Neural compensation has been understood as the "inter-individual variability in the ability to compensate for brain pathology's disruption of standard processing by using brain structures or networks not normally used by individuals with intact brains" (Stern, 2009, p.2016). Neuroimaging studies have found that older participants used more compensatory or alternate brain networks while performing challenging cognitive tasks as a way to maintain their performance (Stern, 2012, 2011, 2005). In support of these findings, many studies have found that individuals with high CR were able to cope better with more extensive brain damage before clinical impairments become apparent (Stern 2012, 2005; Tucker & Stern, 2011; Valenzuela & Sachdev, 2009; Snowdon, 2003). These findings may be understood when considering that these high CR individuals use efficient or alternate brain networks as a way to improve performance (Stern, 2009).

Efficiency and compensatory abilities in high CR individuals have been associated with a delay of the“point of inflection,” which is a term for the time when the individual starts to notice cognitive deficits (Stern, 2009). Therefore, CR has been shown to help individuals tolerate brain pathology in its incubatory period until the point of inflection. Longitudinal studies with Alzheimer’s disease (AD) patients have reported a shorter interval of time between the point of inflection and complete loss of cognitive function in patients with a low CR than in those with a high CR. Comparing CR and BRC, Stern (2012, 2009, 2006) has suggested that individuals with high BRC more quickly reach the point of inflection than those with high CR. Although the point of inflection appeared late in high CR individuals, studies have shown that the rate of decline was faster and the outcome was poorer for high CR than for those with a low CR (Stern, 2012). For example, studies of AD patients have noted that those with high CR died more quickly after the point of inflection and the loss of cognitive function than those with a low CR (Stern, 2009). This is represented in Figure 1 drawn by Stern (2009).

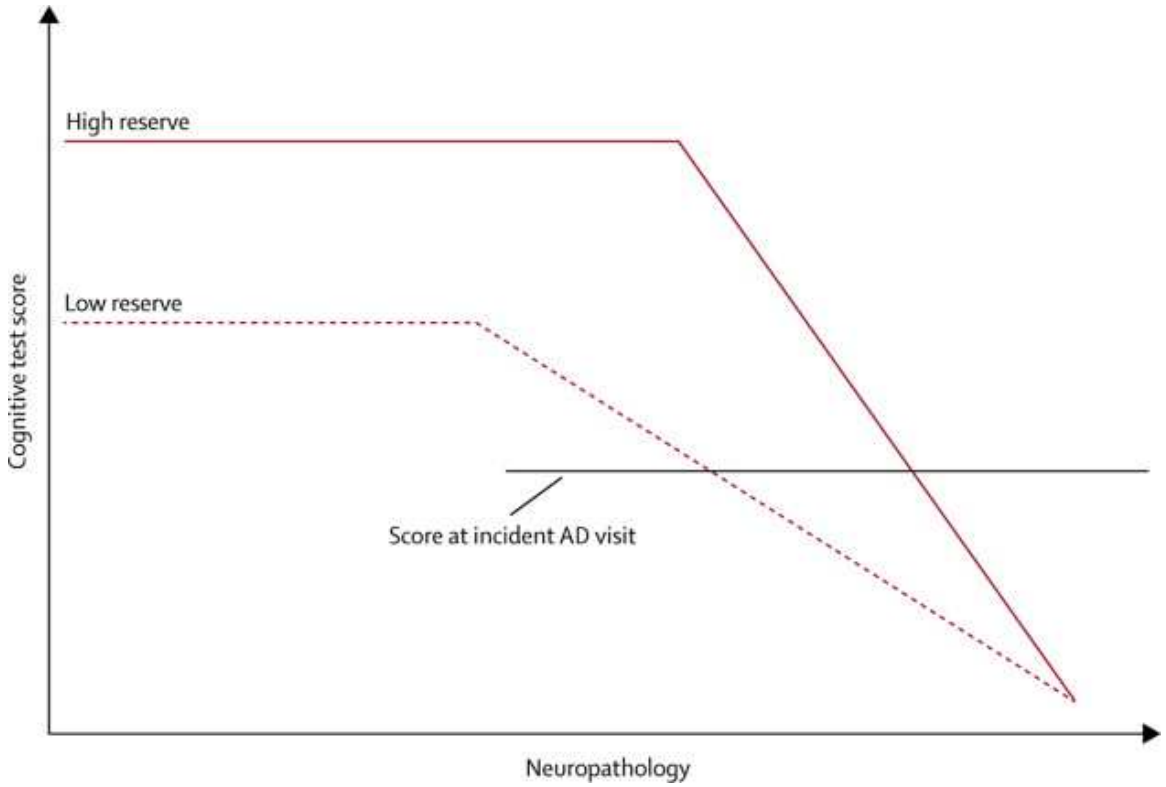


Figure 1: The Point of Inflection and the Loss of Cognitive Function in AD Patients

Some studies have reported contradictory findings on the mediatory function of the CR as well as on the rate of cognitive decline in persons with a high CR. For example, Tuokko and colleagues (2003) have explained a low incidence of dementia in high CR individuals with the ascertainment bias theory (i.e., the use of inappropriate normative standards for identifying a phenomenon in a certain group). In addition, Singh-Manoux and colleagues (2011) found that the rate of cognitive decline was not significantly different between reserve groups except with the occupation variable, where there was some evidence of greater decline in high occupation group.

The relationship between these two models of reserve (CR and BRC) has not been studied and explained by researchers. Stern (personal communication, 2013) has noted that

CR might be involved on one of two levels. The author has suggested that exposures to enriched environment could facilitate the neural circuitry. On the other hand exposures that facilitates CR could eventually lead to changes in the brain itself that would be classified as BRC. Stern (2013) has supported his argument by studies on adult cognitive plasticity. For example, Lovden and colleagues (2010) have indicated that plasticity was the capacity for reactive changes in functioning (e.g., cognitive performance) and for a mismatch between supply and demand. The relationship between CR and BRC appears to be a bidirectional interaction that needs more investigation. Other researchers have proposed different theories to explain why some older individuals perform exceptionally well on challenging cognitive tests.

Gerontological and cognitive neurological researchers have suggested the concept of "super-aged" as a way to explain how interaction between nature and nurture creates differences in coping with brain damage. For example, Guela and colleagues (2010) have reported how some adults over 80 years old outperformed in memory tests by scoring at the level of individuals of 50. These researchers have found that life style and genetics factors may have probably helped super-aged individuals to have high performance. In addition, this study found that individuals who had high performance in memory tests had few tangles in the brain. In this sense, these researchers have suggested that the understanding of anatomic, pathological, genetic, and molecular characteristics of super-aged individuals may contribute to finding what could protect the normal brain from age-related cognitive decline (Guela et al, 2010).

Other researchers have suggested different models of reserve, which are motivational reserve (MR) and emotional reserve (ER). Forstmeier and Maercker (2008) have developed the concept of motivational reserve (i.e., sets of motivational and cognitive abilities that help individuals to become resilient when experiencing brain damage) as a model which includes motivational abilities, such as the regulation of motivation with its different processes, such as decision regulation, motivation regulation, activation regulation, and self-efficacy. These authors have empirically tested two factors of MR: goal orientation and action planning. For example, Forstmeier and colleagues (2012) have found a low risk of mild cognitive impairment and of AD in ApoE e4 carriers in midlife motivational reserve individuals.

In addition, some researchers (Sela-Kaufman, et al., 2013) have introduced another psychological reserve model, which is termed emotional reserve (ER). This model proposes premorbid personality constructs such as early attachment styles (e.g., secure attachment, avoidant attachment, and anxious/ambivalent attachment), personality traits (Neuroticism, Extraversion, Openness to experience, Conscientiousness, and Agreeableness), and temperament (e.g., Emotionality, Activity, Sociability, and Shyness) as resilient factors which differentiate individuals on how they cope with health issues and pathology. For example, Sela-Kaufaman and colleagues (2013) found that certain premorbid personality characteristics (neuroticism, extraversion, conscientiousness, and avoidant attachment style) were moderators in the effect of injury severity on the post-traumatic brain injury outcome. It could be concluded that the involvement in the activities that increase psychological (e.g., cognitive, motivational, and emotional reserve) and neurological reserve models (e.g., brain and cognitive reserve) continually predisposes the brain to different types of learning.

2.2. CR and Brain

The understanding of the concept of learning in the context of cognitive neuroscience can be important in explaining how the reserve construct constitutes resilience in the brain. Experts have defined learning as a process through which "changes in behavior arise as a result of experience interacting with the world" (Gluck, Mercardo, & Myers, 2008, p.2). Neuroimaging studies have showed that every instance of learning entails physical changes in neural circuits such as the neurons' shape, size, and the number of connections to other neurons (van Praag, et al., 2005). Therefore, learning strengthens connections between neurons and how they fire. Lack of learning has been associated with weakening of connections between neurons. It is in this line that Hebb's rule indicates "neurons that fire together, wire together" (Gluck, Mercardo, & Myers, 2008, p.77)

Studies have noted that different facets of CR (e.g., education, occupation, leisure activities) may contribute to learning and changes in the physiology of the brain. For example, one of the neuron's structures that is more involved in the change due to learning is the synapse. Evidence has shown that synapses become strong only when there is a conjoint activity from the presynaptic and postsynaptic neurons. This conjoint synaptic activity has been involved in synaptic plasticity, which is known as the ability of the synapse to change with experience (Gluck, et al., 2008). Therefore, learning has been shown to improve both synaptic plasticity and neuroplasticity (i.e., brain's ability to change as result of experience).

Learning has been found to lead to multiple regenerative mechanisms such as metabolic compensation, collateral sprouting, and neurogenesis. Investigating collateral sprouting (i.e., the growth of new axon branches from terminal ends of healthy or injured

neurons into denervated areas), Gardiner and colleagues (1984) found that exercise training improved collateral sprouting in mice. In addition, Kozorovitskiy and Gould (2005) have shown that learning was involved in compensation neurogenesis (i.e., process of the generation of new neurons from neural stem and progenitor cells). They have presented the following types of compensation of neurogenesis: local (i.e., in the same area of neuron production), distal (i.e., in a different area of neuron production), and induction (i.e., in an area without high rate of neurogenesis). Gould and colleagues (1999) have also shown that learning increases adult neurogenesis in the hippocampal formation. In this line, studies have found that exercise was beneficial for learning and adult neurogenesis in the hippocampus in mice (van Praag, et al., 2005).

Frequency and intensity of learning have been reported to lead to immediate and long-term physiological changes in the brain. Sachdev and Valenzuela (2009) reviewed experimental research with rodents showing that complex mental activity generates the neurotrophic factors (namely brain-derived neurotrophic factor and nerve- growth factor) and enhance neurogenesis, synaptogenesis (i.e., formation of synapses between neurons), and angiogenesis. Black and colleagues (1990) have found that learning promote synaptogenesis whereas motor activities expedite angiogenesis in the cerebellar cortex of adult mice. In this line, learning has been considered as a "cognitive exercise training" (Valenzuela and Sachdev, 2009) which contributes to cognitive reserve and neuroprotection. Cognitive and physical exercises are both involved in building CR in the brain. Further, neuroimaging methods have been used to identify brain structures involved in CR.

Stern and colleagues (2005) have identified the set of brain regions involved in young and elderly participants while they were completing challenging cognitive tasks. Using the PET-Scan, these researchers have identified age-related brain regions of positive loadings (i.e., regions with concomitant increased flow) which includes the right hippocampus, the posterior insula, the thalamus, the right and left opercula. In addition, they found the following brain regions involved in negative loadings (i.e., regions with concomitant decreased flow): the lingual gyrus, the inferior parietal lobe and the association cortex, the left posterior cingulate, and the right and the left calcarine cortex. Young participants with a high CR had increased activation of brain regions of both positive and negative loadings while elders with high CR had increased expression of the brain regions of the positive loadings. These findings are recognized to demonstrate differences in brain substrates between younger individuals using efficient processing mechanisms versus the compensatory networks used by older individuals (Tuokko, et al., 2003). In the same line, Stern and colleagues (2005) have noted that these brain structures point out anatomical differences between the neural reserve and neural compensation.

2.3. Proxies of CR

Studies have identified many lifetime antecedents and factors influencing cognitive reserve. For example, enriched environment, demographic variables (e.g., financial situation, occupation, and education), intelligence, and leisure activities have been found to be proxies of cognitive reserve.

3.3.1. Impact of Nature and Nurture on CR

Genetic predisposition and environmental factors have been found to influence CR and to account for variabilities in individuals' responses to injury. Richard and colleagues (2007) have reported an association between cognitive function in middle age and the following early childhood genetic and environment factors: uterine environment, parents' cognitive ability, education, occupation, social class, socio-economic status, and culture as well as home conditions, linguistic environment, and parental encouragement. In addition, these same authors have indicated the importance of birth weight, nutrition, and birth order for future CR. Finally, academic performance in high school, good scholastic performance, aerobic fitness, early and high physical activities have been shown to influence the CR.

Studies have statistically shown how parents' genetic and environmental factors may become lifetime antecedents of CR (Richards, et al., 2007). Richards and Sackers (2003) have shown in a regression model how parental occupation accounted for childhood cognitive function, education, and occupation. In addition, they showed how childhood cognition and education may influence educational and occupational attainment for the participants as adults. For example, this same study has shown that a father's occupation directly affected a child's cognitive ability at 8 years old, which indirectly influenced cognitive ability at the age of 53. The child's cognitive ability at age 8 affected the child's education by age 26 and the person's occupation at age 43. However, they found that the person's education by age 26 did not account for one's cognitive ability at the age of 53. In addition, the person's own occupation at 43 years old did not influence one's cognitive ability at age 53. It should be noted that parental occupation, childhood cognition and educational attainment appeared to be stronger predictors of CR in adulthood. Therefore, an

enriched early environment and an exposure to cognitively stimulating experience may greatly contribute to a person's cognitive ability.

Studies have investigated the heritability estimate (i.e., the proportion of variance in a characteristic that can be attributed to the genetic variation) of some specific cognitive functions (e.g., memory, processing speed, spatial ability and verbal ability and executive functions) with twin, adoption, and family studies (Reviewed by Lee, 2007). Genetic contributions to cognitive reserve have been shown to vary depending on the cognitive function tested; heritability estimates range from 0.4 to 0.6 in elderly twins (Lee, 2007). In other studies reviewed by Lee, he also noted the following heritability estimates of some cognitive functions: executive functions (79%), processing speed (62%), memory component (52%); spatial and verbal ability (32%). Therefore, it may be suggested that genetic and environmental factors both contribute to cognitive functions.

The influence of genes and the environment on general intelligence has been also estimated by longitudinal studies on identical and fraternal twins, biological siblings, and adopted children (Reviewed in Lee, 2007; Kaufman & Lichtenberger, 2006). For example, Kaufman and Lichtenberger (2006) have indicated a higher correlation for identical twins reared together (.86) than for those reared apart (.76) as well as between fraternal twins reared together (.55) compared to those reared apart (.35). In addition, there was higher correlation among siblings reared together (.47) than those reared apart (.24). The correlation was also higher among unrelated siblings brought up together as children (.28) than those reared together as adults (.04). Finally, there were higher heritability estimates of intelligence in children living together with parents (.42) compared with those living apart (.22) or those

adopted children living together with adopted parents (.19). As with other cognitive functions, genes and shared environment are both crucial for intelligence with genetic influence appearing to exert a stronger influence than environmental factors. Nevertheless, Kaufman and Lichtenberger (2006, p.35) have pointed out that the genetic role on IQ is "not only statistically significant" but it is also "substantial."

Some studies have determined the heritability estimates of IQ and the type of cognitive function that are affected by social class, parenting style, ethnicity, age, and maternal environment (Kaufman & Lichtenberger, 2006). For example, behavioral genetic studies have estimated the heritability of IQ to 50% (Plomin & Perill, 1997). In terms of the type of cognitive ability, some studies have shown that verbal abilities were more heritable (76%) than performance (52%). Individuals in the highest social class have a higher heritability of cognitive ability than those in the lowest social class. Related to social class, Kaufman and Lichtenberger (2006) have reported higher heritability among fraternal twins in highest social class (.78) and highly educated families (.74) than in those in the lowest social classes (.30) and less education (.26). In addition, these authors found higher heritability estimates in those participants whose parents had high occupation and an authoritative parenting style than in those whose parents had low occupation and an authoritarian parenting style.

Heritability estimates for intelligence vary according to ethnicity, age, and maternal environment. Comparing the cognitive scores of parents and children living in the United States of America from different ancestries, studies found higher heritability in those with Korean ancestry (.70) followed by Americans of European ancestry (.50) than Americans of

Japanese ancestry (.35). In terms of age, researchers have reported that parents' genes and the childhood family environment are expressed more in adulthood (.40) than in childhood (.20). However, this expression of parental genes and environment decreases as age exceeds 70 years. Finally, prenatal environment has been found to account for a considerable part of the cognitive function previously thought to come from genes and from the shared environment (Lee, 2007; Kaufman & Lichtenberger, 2006). For example, researchers have suggested that good dietary nutrition, exercise, and a positive psychological status in the mother during pregnancy contribute to a higher cognitive function of the child. The mother's use of alcohol, drugs, smoking, and her ingestion of lead have been found to decrease cognitive function.

Studies using intelligence tests have reported the malleability of intelligence in different countries (Kaufman & Lichtenberger, 2006). Researchers have found an increase in IQ in 35 countries from one generation to the next (Flynn, 1987). This gain in intelligence (i.e., the Flynn effect) has been noted more in nonverbal abilities than in verbal abilities and persists through adulthood (Kaufman & Lichtenberger, 2006). Flynn (1987) has attributed this malleability of intelligence more to the environmental factors (e.g., education, socioeconomic status, parent's occupation, and culture) than to genetic factors.

These behavioral genetic contributions to the reserve construct help our understanding of CR. However, these findings appear incomplete until any consider several complex theoretical issues. First, the new area of epigenetic is a new paradigm which examines environmental effects on gene expression. This new area may stimulate researchers to re-examine the gene-environment dichotomy. Second, the dimensionality of intelligence has been debated for many years. Third, the malleability of CR remains a question for future

research knowing that some components of intelligence are malleable. These issues are beyond the scope of this dissertation.

2.3.2. Education

Education has been suggested as a significant proxy of cognitive reserve due to its involvement in changing the brain through various kinds of learning. While high education has been found to be a significant factor which protects against cognitive decline and dementia, low education has been associated with high risk of dementia and cognitive impairment (see Table 1). In reviewing 15 articles on the association between education and cognitive reserve, Valenzuela and Schdev (2005) reported the significant protective effect of high education (46% of risk reduction) in 10 out 15 studies on decreasing the risk of developing AD. Stern and colleagues (2012) have found that individuals with less than 8 years of education were at 2.2 times risk of developing dementia than those with higher education. The present review of articles from 2000 to 2013 has found in 22 out of 24 studies that education is a significant factor in protecting against cognitive decline and the risk of dementia.

Education has been assessed in terms of years of education, premorbid intelligence (IQ), achievement, bilingualism, and literacy (i.e., the ability to read, write and think critically on what was read and written). Experts have also used years of educational experience as a proxy of cognitive reserve. However, researchers still need to clarify whether years of education in various domains of education (e.g., science, liberal arts, laws, and professional training) or the quality of education (Manly, et al., 2005; Manly, Touadji, Tang, Stern, 2003) provide the same change in the brain that may protect an individual against

cognitive decline or to slow dementia. Other studies have shown that literacy was a "more meaningful" predictor of reserve because it more accurately assesses educational experience, strategy, skills, and knowledge than years of education (Manly, et al., 2007). The importance of literacy in assessing cognitive reserve has been demonstrated primarily among members of minority populations (Silva, et al., 2012; Manly, et al., 2005). Other experts have suggested health literacy as another way of assessing education which provides protection against cognitive decline and dementia in elderly individuals (Baker, et al., 2001). In addition, measures of premorbid intelligence or IQ (NART or Weschler intelligence scales) and achievement tests (WRAT III) have been used as estimates of cognitive reserve. However, the use of reading measures (NART and WRAT) as indicators of intelligence has been shown to be "controversial" (Manly, et al., 2007) because these tests present some flaws; for example, they assess verbal stimuli which activate mostly the left side of the brain. Finally, studies have noted bilingualism to be a proxy of reserve because it has been found to delay the onset of dementia in some individuals (Craik, et al., 2010; Bialystock, Craik, & Freedman, 2007).

There is not much agreement on the measure of "high education" and on whether high education provides protective or compensatory effects on cognitive reserve. Studies have not yet determined an agreed-on level when "high education" provides a neuroprotective factor against cognitive decline or dementia. For example, studies have found significant correlation between dementia and high education in patients with more than 6 years education (Ngandu, et al., 2007), 8 years (Roelli, et al., 2009), 12 years (Garibotto, et al., 2012, Puccioni & Vallesi, 2012), 13 years (Kesler, et al., 2003) or 18 years (Pillai, et al.,

2012, Bennett, et al., 2003). Results are also controversial about whether education provides protective or compensatory effects in decreasing dementia or maintaining cognitive functions. Numerous studies have found that education provides protective and compensatory effects on cognitive reserve against the risk of developing dementia (Stern, 2012, 2009, 2006). However, Christensen and colleagues (1997) argued that education may only help in compensating for neurodegenerative changes rather providing protection against them. Although high education provides protective effects in slowing the risk of dementia, studies have reported that individuals with high education have a faster rate of decline in cognitive function after developing dementia (Tucker-Drob, et al., 2009, Roelli, et al., 2009; Scarmeas, Albert, & Stern, 2006).

Table 1: Studies Reporting the Relationship between Education and Cognitive Functions and Dementia.

Author/year	N	Age (range or means/SD)	Education	Measure of education	Pathology involved	Measures of Cognitive Functions	Findings
Garibotto, et al., 2012	51	M=69.1 SD=7.8	12.2 SD=2.7	Years of schooling	AD: ApoE E4 carriers	Global Function: MMSE. Memory: CVLT, RCFT; Visuospatial: RFCT; Speed of information processing: TMT-A & B; Executive Func: Stroop Color-Word Test; Word fluency; Daily functioning: Instrumental activities of daily living (total), Behavioral disorders: Hamilton depression rating and Neuropsychiatric Inventory (total)	Inverse relation between education and occupational and metabolism in the posterior cingulate cortex and precuneus in both E4 and noncarriers, and no significant difference between group.
Foubert-Sanier, et al, 2012	9294	65 and over					Education was associated with BRC. Education, occupation attainment, and leisure activities significantly contributed to CR.
Puccioni & Vallesi, 2012	45	Older=65-79, Younger=18-34	Older=range: 6-18, M=12.1; Younger=9-18, M=13.4		Conflict Resolution and conflict	Stroop blocks, WAIS-R, CR index questionnaire (CRiq);	Cognitive aging accounted for different processing stages, which are influenced

					adaptation		by partially various compensatory factors.
Pillai, et al., 2012		55-90 yrs	6-20 yrs	High education: >18 yrs; Low education: <13 yrs	MCI and early AD	MMSE, Logical Memory II of WMS.	Early education did not protect against AD by increasing cortical thinness.
Craik, et al., 2010	211	Bilingual=77.7 SD=7.9; Monolingual= 72.6	Bilingual=10.6 SD=5.1; Monolingual= 12.6, SD=4.1)		AD	MMSE	Bilingualism were diagnosed 4.3 years later and reported the onset of AD 5.1 years later than the monolingual subjects. Bilingualism contributes to CR.
Tucker-Drob, et al., 2009	690	65-89 yrs	6-20 yrs Mean=13.4 SD=2.7	Years of schooling and vocabulary	Cognitive functions	Reasoning measures: Word Series, Letter Series, and Letter sets; Processing Speed: Field of View measure; and Vocabulary: finding synonym target.	Vocabulary knowledge and years of education (CR proxies) were significantly associated with cognitive functioning but not with rate of cognitive decline.
Roelli, et al., 2009	162	Mean=72.2; SD=8.6 yrs	Mean=7.2; SD=4.8 yrs	High education: >8 yrs	AD and vascular factors (HTN, DM)	MMSE	Patients with education > 8 years had faster decline of cognitive function, support of CR hypothesis.

Garibotto, et al., 2009	242	M=70.9; SD=8.3 yrs	M=9.2 SD=4.2, AD pts: M=10.5 SD= 4.7; aMCI pts: 13.6; SD=3.1. Range= 6-20 yrs		amnestic mild cognitive impairment and AD	Global Function: MMSE. Memory: CVLT, RCFT; Visuospatial: RFCT; Speed of information processing: TMT-A & B; Executive Func: Stroop Color-Word Test; Word fluency; Daily functioning: Instrumental activities of daily living (total), Behavioral disorders: Hamilton depression rating and Neuropsychiatric Inventory (total)	Higher education and occupation attainment reduced the severity and delayed the clinical expression of AD.
Fritsch, et al., 2007	269	76 yrs and older	High Adolescent IQ (AIQ)=15.62 SD=2.10; Lower AIQ: 14.53 SD=1.91; Lower AIQ: 15.60, SD=2.84	Lower AIQ=71 to 105; High AIQ= 106-149. M=100 SD=12	Cognitive functions	The Otis Self-administered Test of Mental Ability, The Modified Telephone Interview for Cognitive Status (TICS-m), Instrumental activity of Daily Living (IADL), Center for Epidemiologic Studies Depression scale (CES-D).	Men with lower AIQ had memory deficit. Low CR may have predicted poorer episodic memory function.

Kemppainen, et al., 2007	25	55-80 years		High education: >15 yrs; Low education: <6 yrs	Mild AD	MMSE, CERAD; Memory: Logical memory I & II of WMS-R; Verbal functions: Category fluency, similarities of WAIS-R; Visuoconstructive: Block design of WAIS-R.	Highly educated with mild AD showed more advanced pathological and functional brain changes.
Ngandu, et al., 2007	2000	65-79	Low educated: 5 or less; High educated: 6 to 8 years	0-5: Low; 6-8: moderate; 9 and more: high ed.	Dementia: AD	MMSE	Low risk of dementia and AD and low ApoE4 noncarriers were found in highly educated.
Hall, et al., 2007	117	75-85		Low: <7; Moderate: 8-11; High: >12	AD	Blessed Information-Memory Concentration Test, WAIS, Flud Object memory evaluation Test, and Zung depression Test	Better memory performance in those at risk of AD.
Bialystock, Craik, & Freedman, 2007	184; 51 bilingual	Over 65		Bilingual vs mono-lingual	AD	MMSE	Bilingual individuals had a delay of 4.1 years in onset of symptoms of AD compared to monolingual.
Scarmeas, Albert, & Stern, 2006	312	81.6; SD=6.8	7.1 SD=4.5		AD	WRAT-3, MMSE	Faster rate of cognitive decline (e.g., executive speed and memory) in incident AD individuals with higher education than those with lower education.

Perneckzky, et al. 2006	109	63.63 SD=9.79	AD group= 10.16 SD=11.09	Schooling years	AD	MMSE	Highly educated can cope with AD longer than less educated.
Le Carret, et al., 2005	20	Over 65		No schooling: 0-5, Short: 6-9; long: 10-12 and university: >12	AD	MMSE, Mattis Dementia Rating Scale; attention; Stroop, TMT A & B; Language: Naming Test, Verbal Fluency; Verbal episodic memory: Grober-Buschke Test (GBT); Visual gnosis: Visual discrimination (VD); Conceptualization ability: Wechsler Similarities Test; Abstract thinking: Raven's Progressive Matrice (RPM).	Highly educated performed poorly on abstract thinking while less educated were impaired in memory and attention.
Bennett, et al., 2005	156	85.9 SD= 6.5	18.1 SD=3.5		Amyloid and neurofibrillary tangles	MMSE	Education was related to the reduction of amyloids with level of cognition but not of neurofibrillary tangles.
Spitznagel & Tremont, 2005	76	74.09 SD=7.12	13. 2 SD=3.07 Range: 5 to 20	Low and high CR from WRAT score	Anoso-gnosia in question-able and Mild AD	WRAT-3, Cognitive Difficulties Sacle (CDS), Modified MMSE.	Low CR associated with greater anosognosia than higher CR.

Daffner, et al., 2005	48	Young= 18-28; middle=45-55; Old= 65-85	>12	Old =16.5 SD=4.2; Middle= 18.9 SD=4.3; Young=15.4 SD=0.6	Cognitive functions	AMNART, Raven's Progressive Matrice, MMSE, Digit Span, Word Fluency, BNT, Logical Memory II delayed WMS III< Benton Visual Retention Test	No difference in age in the processing of novel target stimuli, likely due to high CR (i.e., superior IQ and number of years of education) in the older subjects.
Staff, et al., 2004	92	41.9 SD=10.9	9.80 SD=1.57		Cognitive functions	RPM, Auditory Verbal Learning Test (AVLT).	Education and occupation associated with the maintenance of cognitive function.
Le Carret, et al., 2003	3777	72.97 SD=5.73		No schooling: 0-5, Short: 6-9; long: 10-12 and university: >12	Cognitive functions	MMSE, Benton Visual Retention Test (BVRT), Isaacs's Set Test (IST), Zazzo's Cancelation Task, Wechsler Paired Associate Test (WPAT), Wechsler Similarities Test (WST).	CR variables (education, occupation, and leisure) showed an effect on the neuropsychological tests.
Kesler, et al., 2003	25	21.16 SD=8.8, range=3-14	13.3 SD=1.7, range=10-16.5		Total intracranial volume (TICV) in TBI	American Testing Program (ACT) scores and Premorbid Standard Testing (PST)	Lower post-injury IQ was significantly associated with lower TCIV and greater changes in IQ from pre-to post injury.

Bennett, et al., 2003	130	84.9 SD=6.6; Range=66.2-101.5	18.1 SD=3.6	Neuritic, diffuse plaques and neurofibrillary tangles in AD.	MMSE, Logical Memory I, IIa, Immediate and Delayed Story Recall, Word List Recognition of WMS, BNT, Reading Test, Verbal Fluency, Digit Forward, Backward, and Ordering, SDMT, Number Comparison, Line Orientation, Progressive Matrices	Neuritic plaques, diffuse plaques, and neurofibrillary tangles were strongly associated with cognitive function; education only modified relation of neuritic plaques and diffuse plaques.
Fritsch, et al., 2002	482	74.0 SD=8.2	12.9 SD=3.2	AD	MMSE	Education slows rate of cognitive decline in individuals with AD but education and occupation did not affect the rate in cognitive decline in functional ability.

2.3.3. Occupation as a Proxy of CR

An extensive body of evidence has supported the thesis that different types of occupations contribute to cognitive fitness, have large and durable effects on cognitive functions, and lower dementia risk in elderly individuals. Occupation as one learning process is considered to build connections in the brain and to enhance different cognitive functions (e.g., executive functions, memory, attention, visuospatial skills, processing speed, and language). Stern and colleagues (2012) have reported that individuals with low lifetime occupation were at greater risk of developing dementia than those with higher lifetime occupation. A review of recent articles from 2002-2012 shows that occupational attainment maintains cognitive function in patients with neurological disorders (e.g., multiple sclerosis, amnestic mild cognitive impairment, and Alzheimer's disease) (See Table 2). While occupation is considered as a buffer for neuropathology and its clinical manifestations, low occupational attainment has been found to be a risk factor for dementia and cognitive decline. High occupational attainment has been associated with a faster rate of cognitive decline after the point of inflection in patients with dementia. In these studies, occupation has been investigated either as a variable by itself or in conjunction with education.

One difficulty of using "occupational attainment" in research about cognitive reserve is a lack of agreement among experts about a valid and reliable measure for this concept. Occupational attainment has been measured differently according to the country of the researchers and that country's method of occupation classification. Some research performed in the U.S. has classified occupation using the U.S. Department of Labor's dictionary of occupation titles (DOT), revised 4th edition (1991). For example, Ghaffar and colleagues

(2012) have subdivided occupational attainment into two groups: high occupations (e.g., professional, technical, and managerial) and low occupations (clerical/sales, agricultural/fishery, processing, machine trades, benchwork, and structural occupations). Within the U.S. occupation classification, other researchers have measured occupational attainment by identifying "lifetime" occupation, taking into account the prestige aspect of an occupation measured using the socioeconomic index (SEI) and the 1980 U.S Census Occupational scheme (Fritsch, et al., 2002).

Studies done in Europe have used different classifications, which differ slightly from the U.S. classification. For example, research performed in the U.K. uses either the British Civil Grade of employment (Singh-Manoux, et al., 2011) or the U.K. Office Population Censuses and Surveys' classification. In Spain, Sole-Padulles and colleagues' study (2009) has classified occupational experience in conjunction with educational attainment by coding as follows: qualified manual, qualified non-manual or technician, professional (university degree obtained), and manager or director (university degree obtained). Finally, other researchers have classified occupational attainment following these categorizations: no occupation; unskilled occupation; housewife; skilled laborer, tradesman, lower level civil servant, employee, self-employed small business, office or sales personnel; academician or specialist in subordinate position; and self-employed with a high degree of responsibility (Garibotto, et al., 2011, 2009).

Despite these variances, it remains important in classifying occupational attainment to establish a distinction between occupation/profession and employment/job. Although job and occupation are closely related, job has been defined as the different positions a person can

occupy (e.g., surgeon) while occupation encompasses the entire list of jobs that a person has done related to one's training (e.g., physician). This distinction can help to identify whether a lifetime, present, or past employment can be considered as a variable or the level of a variable for assessing occupation. In addition, this distinction becomes crucial in the context of job instability in an individual's career in modern society. For example, the U.S. Bureau of Labor Statistics (BLS, 2008), the Labor Department has found that the average person changes jobs 10.8 times during a career with an average tenure of 4.1 years. Therefore, the concept of job instability does not consider occupation as a continuous variable (i.e., taking any value on the measurement scale being used) but as an ordinal variable (i.e., ordered categories) through which the association between occupation and cognitive reserve may take into consideration differences between tenures on the scale of occupation.

Table 2: Studies Reporting the Relationship Between Occupation and Cognitive Functions and Dementia.

Author/year	N	Age (range or means/SD)	Education in years	Classification of Occupation	Pathology involved	Measures of Cognitive Functions	Findings
Ghaffar, Fiati, & Feinstein, 2012	72: Low occupation =32, High=40	43, SD=9.7	16, range=13-17	U.S department of Labors' dictionnary of occupational titles (DOT)	Multiple sclerosis	SDM, PASAT, CVLT-II, DKEFS.	MS patients with high occupational attainment performed better cognitively than those with low occupational attainment after controlling for brain atrophy and IQ.
Garibotto, et al., 2011	51	Carriers E4= 69.1 SD=7.8; non-carriers E4= 67.6 SD=9.6	Carriers E4= 11.6 SD=3.3; non-carriers E4= 12.2 SD=2.7	Score ranging from 1 to 6 corresponding to last employment.	Amnestic mild cognitive impairment and AD	Global Function: MMSE. Memory: CVLT, RCFT; Visuospatial: RFCT; Speed of information processing: TMT-A & B; Executive Func: Stroop Color-Word Test; Word Fluency; Daily functioning: Instrumental activities of daily living (total), Behavioral disorders: Hamilton Depression Rating and Neuropsychiatric Inventory (total)	Education and occupation attainments were compensatory proxies for reserve in E4 carriers.

Singh-Manoux, et al., 2011	5234 men and 2220 women	56, SD=6		British Civil Service grade of employment: High: administrative; intermediate: professional or executive; low: clerical or support	Cognitive function	The Alice Heim 4-I (AH4-I); Free Recall of 20 words, Verbal Fluency Test, Mill Hill Vocabulary Test.	Strongest association between cognitive function and occupation; greatest decline in high occupation.
Garibotto, et al., 2009	242	M=70.9; SD=8.3 yrs	Range= 6-20 yrs	Score ranging from 1 to 6 corresponding to last employment.	Amnestic mild cognitive impairment and AD	Global Function: MMSE. Memory: CVLT, RCFT; Visuospatial: RFCT; Speed of information processing: TMT-A & B; Executive Func: Stroop Color-Word Test; Word Fluency; Daily functioning: Instrumental activities of daily living (total), Behavioral disorders: Hamilton Depression Rating and Neuropsychiatric Inventory (total)	High education and occupation AD patients performed better in cognitive tests than those with low education/occupation.

Sole-Padulles, et al, 2009	44	Older 65	0=no formal edu, 1=primary edu, 2=secondary edu, 3=superior or university edu.	0=non-qualified manual, 1=qualified manual, 2=qualified non manual, 3=professional, 4=manager or director.	Brain volume in MCI and AD.	MMSE, Vocabulary WAIS-III	Higher education-occupation and other inferred CR proxies were associated with reduced brain volumes in MCI and AD patients, increased brain function as well as active compensatory mechanisms.
Staff, et al., 2004	92	41.9 SD=10.9	9.80 SD=1.57	UK office of population Censuses and Surveys.	Cognitive functions	RPM, Auditory Verbal Learning Test (AVLT).	Education and occupation associated with the maintenance of cognitive function.
Fritsch, et al., 2002	482	74.0 SD=8.2	12.9 SD=3.2	Socioeconomic status index (SEI) using the 1980 US Census occupational scheme.	AD	MMSE	Education slows rate of cognitive decline in individuals with AD but education and occupation did not affect the rate of cognitive decline in functional ability.

2.3.4. Impact of Physical Activity (PA) on Cognitive Reserve

Numerous studies have reported beneficial effects of physical activity (i.e., any body movement which leads to burning calories) or exercise (i.e., organized or repetitive form of physical activity to strengthen part of one's body and increase cardiovascular fitness). Experts distinguish two types of exercise: aerobic (i.e., person breathes enough oxygen to compensate for the rate of oxygen used) and anaerobic (i.e., person cannot keep up with oxygen while breathing). Aerobic exercises have been shown to be more beneficial to the body than anaerobic exercises (see Table 3). The terms "physical activity" (e.g., walking up stairs, making a bed, moving a lawn, etc.) and "exercise" (e.g., walking, swimming, bicycling, etc.) will be used interchangeably in this proposal. The Mayo Clinic Plan for Healthy Aging (2005) has summarized the following benefits from challenging one's body in adult life: slowing the loss of muscle mass, strengthening the body, reduction of stress, and enhancing mental well being (e.g., decreased risk of depression and anxiety, enhanced mood, self-esteem, and sleep). Findings from the Mayo Clinic (2005) also indicate that moderate exercise (i.e., running 3 miles a day) increases longevity and prevents or slows disease (e.g., cardiovascular disease, hypertension, diabetes, obesity, osteoporosis, arthritis, and cancer).

Physical fitness through exercise has been associated with cognitive fitness, functional abilities in later life, and the slowing of dementia (See Table 3).

Table 3: Studies Reporting the Relationship of Physical Activity (PA) and Cognitive Functions and Dementia.

Author/year	Sample	Age (range or means/SD)	Measures of PA	Types of PA	Length of PA	What was measured	Findings
Gow, et al., 2012	691	72.5 SD=0.7	Self-report questionnaire			Hypertension, CVD, stroke.	PA was associated with neuroprotective factor as larger gray matter and normal-appearing white matter volumes, and fewer white matter lesions.
Varela, Ayan, Cancela, & Martin, 2011	48	65 and older	3 times 30 mins walk a week for group A and 20 mins cycling for group B, and recreational activities for group C	Aerobic exercise	6 months	Cognitive level and functional ability in Mild Cognitive impairment (MCI)	Aerobic exercise improved cognitive level and functional ability but intensity was not a factor.
Baker, et al., 2010	33 (17 women)	55 to 85 years old	Modified Balke maximal-graded trademill test, 4 days a week to 60 mins per session.	High aerobic exercise	6 months	Amnestic mild cognitive impairment, glucose metabolism, lipid, adiposity, cortisol, BDNF, IGF, and Beta-amyloid.	Aerobic exercise improved CF (executive control of multitasking, cognitive flexibility, information processing efficiency, and selective attention), glucose metabolism, hypothalamo-pituitary-adrenal axis, and tropic activity more so for women.

Erickson, et al., 2010	299	78 mean age	Walking amounts ranged from 0 to 300 blocks (mean 56.3; SD 69.7)	Aerobic exercise	13 years	Gray matter volume and cognitive deficits.	Significant association between gray matter volumes of frontal, occipital, entorhinal, and hippocampal regions and walking 72 blocks (6-7 miles per week), which reduced cognitive deficits after 9 years. (But no effect after more than 72 blocks)
Geda, et al., 2010	198 with MCI from 1126 normal	50-65 years	Self-report questionnaire	Aerobic exercise	Within 1 year	Mild Cognitive Impairment (MCI)	Midlife and late life moderate exercise decreased MCI.
Rovio, et al, 2010	75	65-79 years	Self-report questionnaire on midlife PA	Aerobic exercise	Re-examined after 21 years	Structural brain changes in control, MCI, and dementia	No significant correlation between midlife PA and severe white mater lesions later in life.
Bugg & Head, 2009	52 healthy adults	55-79	Self-report questionnaire in running, walking, and jogging. Intensity: low, moderate, high exercise	Aerobic exercise	Estimation over past 10 years	Volume estimates in PFC, parietal, temporal, occipital, neostriatal, and medial temporal regions.	High exercise was significantly associated with maintenance of medial temporal lobe integrity.
Dubbert, et al., 2009	944 African American (AA)		Self-report PA		6 years	Subclinical Cerebral infarcts from atherosclerosis	In AA sample, there was inverse correlation between sport PA and subclinical MRI-detected cerebral infarcts after 6 years.

Dik, Deeg, Visser, & Janker, 2007	3107	55 to 85 years old	Self-report of PA between 15 to 25 years old in categories: Never, low (less than 1 hr a week), moderate (3 to 9 hrs per week), and high (10 hrs or more a week).	Aerobic exercise	3 to 6 years follow up	Global cognitive function and Information Speed Processing	Association between early PA between 15 and 25 years old with information speed processing in older age in men but not with global CF. No association for women.
Etnier, et al., 2007	90 older women	51-81 years	Self-report questionnaire using modified Baecke questionnaire	Aerobic fitness		ApoE-E4 Genotype	Stronger effect of aerobic exercise on memory performance in those at risk with AD.
Deary, Whalley, Batty, & Starr, 2006	460	Age 11-79	6 meter walk walk time; grip strength, function function volume	Aerobic exercise		Cognitive Functions (CF)	Fitness measures were associated with CR at age 79.
Weuve, et al., 2004	18766 women	70 and older	Self-report activities (e.g., Running, walking, jogging, yoga, etc.)	Aerobic exercise	>20 minutes daily	Cognitive Functions	Long-term PA significantly correlated with better cognitive function and less CF deficit.

A number of studies have indicated that aerobic exercise was correlated with improved performance in cognitive function (Verala, et al., 2011; Baker, et al., 2010, Erickson, et al., 2010; Deary, et al., 2007; Weuve, et al., 2004). A meta-analysis of 44 studies reported an overall effect size of 0.32 for the association between exercise and cognitive function (Voss, et al., 2011). This good cognitive performance after regular exercise has been reported in specific cognitive functions such as executive functions, selective attention (Baker et al., 2010), information processing speed (Baker, et al, 2010; Dik, et al., 2007), and memory (Voss, et al., 2011). Smith and colleagues (2010) have reported the following Hedges' g standard effect size (i.e., the estimated magnitude of the relationship between the data and its reflection in the population) for different cognitive domains: Attention/speed (g=0.158); executive function (g=0.123); working memory (g=0.032), and memory (g=0.128). Other meta-analyses have found a small to medium effect size of physical activity on perceptual skills (d=0.49), IQ (d=0.34), and verbal ability (d=0.17) (Voss, et al., 2011). It is important to note that many of these studies used less sensitive measures (e.g., Mini-Mental Status Exam) to assess global cognitive functions.

In addition to improving brain function, the anatomy of brain structures appeared to be improved by aerobic exercise (Reviewed in Voss, et al., 2011). Studies have indicated that individuals engaged in moderate aerobic exercise had larger gray matter in the frontal, occipital, entorhinal, and hippocampus regions (Varela, et al, 2011), a reduction of white matter lesions (Gow, et al., 2012) and good maintenance of the medial temporal lobe compared to individuals who did not exercise at all. Many of these brain structures are known to be involved in cognitive functions (e.g., memory, executive functions, attention,

and information processing speed). Physical activity has been found to increase glucose metabolism, cortisol level (Baker, et al, 2010), neurogenesis in the hippocampus, angiogenesis (Voss, et al., 2011), a brain-derived neutrophic factor in the hippocampus (i.e., BDNF, which is a protein in the family of growth factors), the size of the dentate gyrus, and a serum insulin growth factor (i.e., IGF, a protein in family of sulfation factor).

Exercise has been reported to reduce homocysteine (i.e., a non-protein amino acid), APOE e4 carriers gene expression (Rockwood & Middleton, 2007), and slowing the amyloid plaques formation that is involved in the pathology of AD. This may explain why regular aerobic exercise has been associated with slow risk of mild cognitive impairment (MCI), Alzheimer's disease (AD), and other dementias. For example, meta-analyses have found significant reductions of cognitive impairment after physical exercise (Rockwood, et al., 2007). Geda and colleagues (2010) have reported the beneficial impact of moderate physical exercise in late life on both normal cognition and MCI. In their meta-analysis of 16 prospective epidemiological studies, Hamer and Chinda (2009) have reported that high exercise was associated with the reduction of the risk ratio for dementia (0.72), AD (0.55), and Parkinson's disease (0.82).

Some studies have identified various moderator variables of the relation between exercise and cognitive function or dementia (e.g., type, duration, intensity, and frequency of exercise and age of fitness program onset as well as gender of the participant). Some studies have found that a variety of physical exercise was more beneficial to improving cognition and lowering dementia instead of concentrating on a single physical activity (Rockwood & Middleton, 2007). In addition, researchers have shown that the duration or intensity of

physical activity modify factors neuroprotective effect of exercise on dementia or cognitive function.

However, it is important to note that documented published evidence has not reached unanimity about the use of the concepts “beneficial”, “moderate,” or “high level” of exercise when assessing the duration and intensity of exercise. Some researchers have subdivided the duration or the intensity of exercise into three levels: high exercise (i.e., at least 30 minutes of aerobic exercise and at least 3 times a week), low exercise (i.e., less than 30 minutes of aerobic exercise and less than 3 times a week), and no exercise (Rockwood & Middleton, 2007). Results of studies are inconsistent about the association between the duration or intensity of exercise and dementia or cognitive functions, with some finding no correlation but others finding significant correlations. For example, some studies found low cognitive scores in groups of individuals who had low or high exercise (Lytle et al., 2004).

The age and gender of the fitness program participants have been found to influence the relationship of exercise to cognitive function or dementia. For example, findings on the age of fitness program participants have found contradictory results. Some studies have reported the most beneficial impact of early exercise on cognition or dementia for participants between 15-25 years old (Dik, et al., 2007), others for midlife exercise (Rockwood & Middleton, 2007), and others for late life exercise. In terms of gender, some studies have found that high exercise was protective against cognitive decline or reduced the risks for dementia in both men and women (Mayo clinic study, 2005), men (Simons, 2006) or women only (Etnier, et al., 2007; Laurin, et al., 2001). Some of the ongoing challenges of research on the relationship between exercise and cognitive function or dementia appear to

lie in the methodological approaches (i.e., use of self report questionnaires and adherence to exercise). These approaches reveal the challenges such as social desirability, need for social approval, and a tendency to agree with items (Kadzin, 2003).

2.3.5. CR and Leisure Activities (LA)

Participation in intellectually stimulating leisure activities has been considered as a significant proxy of cognitive reserve. Studies have presented exhaustive lists of leisure activities that stimulate the brain and contribute to cognitive reserve: reading (e.g., newspaper, magazine or a book); playing games (e.g., chess, bridge, Scrabble, cards, and Monopoly); solving crossword puzzles (e.g., Soduko, acrostics, and anagrams); doing art (e.g., drawing, painting, sewing, and sculpting); ongoing training (e.g., taking a course, participating in a discussion, or a conference); participating in the activities of daily living (e.g., preparing a meal, financial management, housekeeping, and transportation); attending church or religious activities, and playing or listening to musical instruments (Nucci, et al., 2012; Mortinez, Borenstein, & Schinka, 2003; Wilson, et al., 2003). Stern and colleagues (2012) have reported that individuals involved in six or more leisure activities were found to have 38% lower risk of developing dementia than those with lower participation in leisure activities.

Greater participation in leisure activities has been associated with an improved cognitive performance and a reduction of risk for Alzheimer's disease and its clinical manifestations. For example, researchers have reported that low diversity and frequency in leisure activities were predictors of decreased working memory (Ruiz-Contreras, et al., 2012) while a high cognitive life style was found to be correlated with improved performance in

neuropsychological assessments (Marioni, et al., 2012; Reed, et al., 2011, Suchy, et al., 2011). Playing musical instruments, writing and listening to music have also been associated with brain plasticity and cortical reorganization, mostly in sensorimotor functions, verbal memory, auditory learning, language functions, and visuospatial abilities (Hanna-Pladdy & Mackay, 2011). These protective effects of musical activities could be understood by the fact that musicians use multiple abilities in the brain such as motor functions, auditory functions, and reading musical notes (Hanna-Pladdy & Mackay, 2011). Finally, frequent involvement in leisure activities has been associated with the reduction of risk of AD (Akbaraly, et al., 2009; Helner, et al., 2007, Scarmeas, et al., 2003, 2001; Crowe, et al., 2003; Verghese, et al, 2003) and multiple sclerosis (Sumowski, et al., al., 2010).

Studies have shown that the number, intensity, meaning, frequency, and duration of leisure activities are important predictors in making a leisure activity a candidate for improving cognitive activity (Shinka, et al., 2005). In terms of numbers and frequency of leisure activities, Ruiz-Contreras and colleagues (2012) found that a low diversity and a low frequency of cognitive activities were indicators of poor performance in working memory. In regard to quantified activities, researchers still have to figure out whether activities that have more social, leisure, or physical elements contribute differently to the cognitive reserve due to their cognitive demand. In addition, the years of formal training and the duration of leisure activities have been indicated as predictors of cognitive reserve (Hanna-Pladdy & Mackay, 2012). Changes in life situations have been suggested to contribute to changes in the patterns and intensity of cognitive challenge (Schinka, et al., 2005). Finally, the age of acquisition of the ability to play has been inconsistently reported to influence cognitive reserve. For

example, Hanna-Pladdy and Mackay (2012) have found that the age of musical instruments acquisition was a significant predictor of performance for immediate and delayed recall in musicians. Some studies have found that current (i.e., one month or 6 months before the interview) leisure activities participation (LeCarret, et al., 2003, Scarmeas, et al., 2001, 2003), young adulthood, middle life and late life leisure activities participation (Marioni, et al., 2012), and daily and monthly leisure activities participation (Akbaraly, et al., 2009) are associated with improved cognitive reserve. However, studies still have to determine the duration, frequency, age, and stage of participation in leisure activities which contribute in an efficient and compensatory way in maintaining cognitive function. Frequent involvement in stimulating leisure activities has been reported to improve cognitive function and to reduce the risk of developing dementia (See Table 4).

It is along these lines that researchers have developed cognitive activities scales, which validly and reliably measure leisure activities that contribute to CR and which measure them in terms of frequency, duration, and intensity. Some of the well-known measures are the Cognitive Activity Scale (Wilson, 1999), the Florida Cognitive Activities Scale (Mortinez, Borenstein, & Schinka, 2003), and the Cognitive Reserve Index questionnaire (Nucci, Mapelli, & Mondini, 2012). The Cognitive Activity Scale (CAS) is a brief test covering seven leisure activities (i.e., telling a story, visiting a library, reading a newspaper, reading a magazine, reading a book, writing a letter, and playing a game) on a five-point frequency scale (5: every day or about every day; 4: several times a week; 3: several times a month; 2: several time a year; 1: once a year or less) which includes age reference (i.e., 6, 12, 18, 40, and present). Wilson and colleagues (2003) have found that the item-total

correlation ranged from .10 to .60 (median r=.40) with Cronbach's coefficient alpha of 0.88, which indicates a good (high) degree of internal consistency. These findings suggest that CAS "could adequately summarize frequency of activity participation across the life span" (Wilson et al., 2003, p.636). Researchers have identified some flaws in the design of CAS such as its brevity (seven items only) and an "extremely low response frequency" in the item "visiting the museum" (Schinka, et al., 2005).

The second cognitive scale developed to assess stimulating leisure activities through life span is the Florida Cognitive Activities Scales (FCAS). The FCAS is longer test of leisure activities (25 items) than the Cognitive Activity Scale (CAS) but the FCAS has three items in common with the CAS (playing games, reading a newspaper and reading books or short stories). This measure is designed for an aging population and uses a likert scale frequency (0: never did this activity, used to do but not in the past year, 1: less than 1 time per month; 2: 1-4 times per month; 3: 5 or more times per month, but not every day; 4: every day). The FCAS includes three composites: Higher Cognition (HC), which includes 11 items; Frequent Activities (FA), which contains 8 items; and Cognitive Activities (CA), which has 6 items. The FCAS has a questionable internal consistency reliability (alpha of .65) and correlates moderately with the years of education of the participants and neuropsychological tests. Some of the shortcomings of the FCAS are the confusing use of likert scale (e.g., the use of two zeroes in this scale) and imprecision about when an activity was carried out during a life span.

The third measure developed to evaluate cognitive activity is the Cognitive Reserve questionnaire index (CRiq). The CRiq is a self-report measure, standardized on an Italian

sample, which includes three proxies of CR: education, working activity, and leisure activities (Nucci, Mapelli, & Mondini, 2012). The CRI-Leisure Time scale includes 17 items, which are categorized activities with weekly frequency (five items); monthly frequency (6 items); annual frequency (3 items); and fixed frequency (3 items). The CRI-Leisure Time composite contains four items which are similar to both CAS and FCAS (e.g., reading newspapers and magazines, playing musical instruments, playing game, and writing letters) and nine items in common with FCAS (e.g., reading newspapers and magazines, reading books, housework activities, driving, social activities, using new technologies, artistic activities, and participating in exhibitions, concerts, and conferences). The CRiq has an acceptable internal consistency of 0.77 for CRI-education, 0.78 for CRI-working activity, and 0.72 for CRI-leisure Time. Although CRiq has a high internal consistency reliability, it is important to note that few studies have used this measure for an American population. This measure of cognitive activity inquires about the frequency of activities in only two ways: "never/rarely" versus "often/always." Finally, this measure does not list some items which have high frequency in the U.S and which could contribute to CR (e.g., walking or driving in unfamiliar places requiring a map, managing a financial portfolio of investments, and attending church or religious activities).

Table 4: Studies Reporting the Relationship Between Leisure activities and Cognitive Functions and Dementia.

Author/year	N	Age in years	Education in years	Measure of leisure activities	Pathology involved	Measures of Cognitive Functions	Findings
Zendel & Alain, 2012	Musicians =74; Nonmusicians= 89	18 and 91		At least 6 years of formal music lessons.	Hearing sensitivity	Audiometer, QuickSIN test (Speech in noise version 1.3).	Musicians did not show much age-related decline in some auditory tasks and demonstrated a lifelong advantage in mistuned harmonic detection.
Ruiz-Contreras, et al., 2012	93	23.68, SD=2.67; Range=21-30	16.45, SD=1.85; Range= 12-20.5	Self-report questionnaire of 13 items on Yes or No. Diversity and frequency	Working memory	Working memory: n-back task	Low diversity and low frequency was associated with reduced working memory efficiency.
Marioni, et al., 2012	13004	65 and over		Cognitive lifestyle score from edu, occupation, cognitive lifestyle activities in 3 phases: young adulthood, midlife, and late life.	Cognitive recovering	MMSE over 16 years.	High cognitive lifestyle was associated with an improved score on MMSE.

Hanna-Pladdy & MacKay, 2011	70	60-83	nonmusicians=16.2, SD=2.5; Low musicians: 17.4, SD=2.2; High musicians= 17.6 SD=2.6	3 groups: nonmusicians; low activity musicians: 1-9 years; high activity musicians: >10 years	Cognitive aging	Premorbid verbal intelligence: American Adult Reading Test (AMNART), Memory: CVLT-II, Visual Reproduction I & II subtests of WMS-III; Auditory attention: Digit Span of WAIS-III; Auditory working memory: Letter-Number Sequencing of WAIS-III; Visual attention: Spatial Span of WMS-III; Cognitive flexibility: Trails A&B; Language: BNT.	High musical activity throughout lifespan was a strong predictor in the maintenance of cognitive aging (e.g., nonverbal memory, executive processes, naming).
Reed, et al., 2011	652 autopsied cases	87, SD=6.67	16.76, SD=3.69	A 5-point Scale of Self-report activity.	AD markers, Lewy body, infarcts, microinfarcts, and brain weights	Working, episodic and semantic memory, Verbal Fluency, Visuospatial ability, and Perceptual speed.	Leisure cognitive activities throughout adulthood (40 years and above) were stronger predictor of reserve than education.

Suchy, Kraybill, & Franchow, 2011	75	70.23, SD=6.8, range=60-87	14.44, SD=2.65, range=10-22	IADL scale: communication, financial management, housekeeping, and transportation	Cognitive Reserve	Information subtest of WAIS-III.	Better IADL performance was associated with better performance in cognitive tests and better awareness of IADL weakness was associated with higher levels of CR, but lower levels of executive abilities.
Sumowski, et al., 2010	36	Over 25	16 SD=2,.3	Questionnaire in cognitive activity after 20 years old.	MS	SDMT, Open-trial selective reminding test.	MS patients who engaged in more cognitive leisure were able to resist more severe brain atrophy at given cognitive status.
Akbaraly, et al., 2009	5698	65 and over		Self-report frequency questionnaires: daily and monthly.	Dementia	MMSE	Stimulating leisure activities (LA) were associated with a reduced risk of dementia.
Helner, et al., 2007	283	M=79	7 SD=4.5	4 categories: intellectual, social, physical, and other	AD	Selective Reminding Test, Similarities subtest of WAIS-R, Rosen Drawing Test, Benton Visual Retention Test, BNT.	Greater participation in prediagnosis leisure activities was associated with faster cognitive decline.
Wilson, et al., 2003	159	83.5 SD=5.5	14.7 SD=3	Cognitive activities frequency at age 6, 12, 18, 40, and current age.	Cognitive function	MMSE, Word List Memory and Recall, Immediate and Delayed Recall East Boston Story, Logical Memory of WMS, BNT, Verbal Fluency, Digit Span Forward and	Cognitive activity was correlated with better scores in perceptual speed, visuospatial ability, and semantic memory but not with episodic or working memory.

						Backward of WAIS-III, SDMT, Judgment of Line Orientation Spatial Ability.	
Scarmeas, et al., 2003	25: 9 pts and 16 healthy.	AD pts: 68.8, SD=14.9; Control: 76.6, SD=6.3	AD pts: 15 SD= 3.5); Control: 15.3 SD= 2.0	Questionnaire of activities engaged in the last 6 months: Never, sometimes, often	Cerebral blood flow (CBF) in AD.	Nelson Adult Reading Test (NART), Modified mini-mental state (mMMS), Selective Reminding Test (SRT), Phonological and Categorical Fluency.	Negative correlation between previous reported activity score and CBF in AD patients.
Crowe, et al. 2003	214	77 SD=8.0		Questionnaire on 11 leisure activities practiced before 40.	Risk of AD	MMSE	Participation in a greater overall number of leisure activities was associated with reduced risk of AD and dementia in general.
Le Carret, et al., 2003	3777	72.97 SD=5.73		Score calculated on number of leisure activities participated by time of interview.	Cognitive functions	MMSE, Benton Visual Retention Test (BVRT), Isaacs's Set Test (IST), Zazzo's cancelation Task, Wechsler Paired Associate Test (WPAT), Wechsler Similarities Test (WST).	CR variables (education, occupation, and leisure) showed an effect on the neuropsychological tests.
Verghese, et al., 2003	469	Older than 75	8 or less	Interviews on participation in 6 activities:	Risk of AD	Blessed Information-Memory Test, Flud Object-Memory	Reading, playing board games, playing musical instruments, and dancing were associated with

				reading books, writing for pleasure, doing cross-word puzzles, playing board games, participation in discussion, and playing musical instruments.		Evaluation, IQ.	reduced risk of dementia.
Scarmeas, et al., 2001	1772, 207 became demented	Incident of dementia: 78.2, SD=6.5; No incident of dementia: 75.3, SD=6.2	Incident of dementia: 7.1, SD=4.5; No incident of dementia: 8.7, SD=4.5	Self-report questionnaire of 13 items performed during the month before interview.	Incidence of AD	Selective Reminding Test (SRT),	Risk of dementia was decreased in individuals with high leisure activities.

2.4. Summary on CR

In summary, different types of reserve and their various proxies were discussed in this chapter. Stern (2012, 2009, 2006, 2002) has suggested two important models of reserve: passive (i.e., brain reserve capacity) and active (i.e., cognitive reserve). Other researchers have proposed two other components of reserve: motivational (Forstmeier and Maercker (2008) and emotional (Sela-Kaufman, et al., 2013). However, future studies have to establish the relations between the passive and the active models of reserve and to determine whether the reserve construct is malleable. In terms of clinical assessments of cognitive reserve, Stern (2012, 2009, 2006, 2002) has proposed IQ/estimate IQ, education, occupational attainment, physical activity, and leisure activities as proxies for cognitive reserve. It has been noted that frequency, duration, variety, complexity, and a high level of life experience were significant predictors of reserve. However, researchers have still to determine the effective frequency, duration, variety, complexity and the level of a high classification of these proxies to help individuals in clinical settings.

Proxies of cognitive reserve have been used in different studies either separately or synergistically due to significant contributions of each proxy to the reserve (Stern, 2009). For measures of CR proxies, Stern (2012) has proposed the use of more challenging assessments that are more specific for a particular neuropathology in order to capture cognitive changes and cognitive reserve. For example, the use of associative learning and crystallized measures have been found to capture reserve effects well. In addition, the use of matched control and treatment groups has been suggested to compare whether CR affects the rate of decline. It has been proven that the use of dichotomous outcome (presence or absence of pathology) and

both global and specific measures as well as continuous measures contribute significantly to statistical power (Stern, 2002).

Only a few pathologies have been used to test the reserve construct. Many studies have used dementia, mostly Alzheimer's disease (Stern, 2009; Valenzuela & Sachdev, 2006), multiple sclerosis (Sumowski, et al., 2009), Parkinson's disease (Glat, et al., 1996), HIV dementia (Shapiro, et al., 2014, Farinpour, et al., 2003), Memory complaints (Lojo-Seoane, et al., 2014), traumatic brain injury (Kesler, et al., 2003), schizophrenia, bipolar disorder (Barnett et al., 2006), depression (Martino, 2008), vascular injury (Elkins, et al., 2006; Dufouil, et al, 2003), and coronary artery disease (Ropacki, et al., 2007). However, the relation between CR and pathology is not a causal but an associative or correlational relation (Stern, 2009).

CHAPTER 3: CLINICAL HYPERTENSION AND SLOW VASCULAR COGNITIVE DECLINE

3.1. Pathophysiology of Hypertension

3.1.1. Definition and Classification of Hypertension

Arterial blood pressure is one of the most important vital signs which clinicians measure in case of emergency or regular medical consultation. In measuring the arterial blood pressure, clinicians osculate both the maximal (i.e., systolic) and the minimal (i.e., diastolic) pressure that the left ventricle of the heart exerts on the wall of blood vessels for sending blood to the rest of body. The heart is said to be in systole when the artery becomes elastic and stretches to eject blood from the heart to the body. However, during the diastole, the elasticity of the artery brings the artery to its normal width in order to maintain blood pressure within the vessel (McCance, Huether, Brashers, & Rote, 2010). Although experts do not have a clear consensus on the level of abnormal blood pressure (Kaplan & Victor, 2011), clinicians have considered hypertension as "an arterial pressure greater than 140/90 mm Hg in adults on at least three consecutive visits to the doctor's office" (McPhee & Hammer, 2010, p.301). The American Heart Association (2012) has categorized blood pressure (BP) as shown in Table 5.

Table 5: Classification of Blood Pressure According to the American Heart Association (AHA, 2012).

Blood Pressure	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	less than 120	and	less than 80
Prehypertension	120-139	or	80-90
Hypertension 1	140-159	or	90-99
Hypertension 2	160 or higher	or	100 or higher

Hypertensive crisis	Higher than 180	or	Higher than 110

Experts distinguish primary hypertension from secondary hypertension. Primary hypertension, also called essential or clinical hypertension is idiopathic hypertension with an unidentifiable cause. On the other hand, secondary hypertension is related to an identifiable cause (McPhee & Hammer, 2010). For example, the following diseases have been considered to be leading causes of secondary hypertension: renal diseases (e.g., renal parenchymal, acute glomerulonephritis, chronic nephritis, polycytic disease, diabetic nephropathy, hydronephrosis), endocrine diseases (e.g., acromegaly, hypothyroidism, hyperthyroidism, hypercalcemia), neurological disorders (e.g., increased intracranial pressure, quadreplegia, acute porphyria, lead poisoning, and Guillain-Barre Syndrome), renovascular diseases, renin-producing tumors, primary hyperaldosteronism, Cushing syndrome, pheochromocytoma, coarcotation of the aorta and aortitis, pregancy, and estrogen use (Kaplan & Victor, 2011; McPhee & Papadakis, 2012). In terms of estimated frequency, McPhee and Hammer (2010) have reported that essential hypertension represents 88% of hypertension in the hypertensive population while secondary hypertension represents 12% of the general hypertensive population (McPhee & Hammer, 2010). This study will address primary hypertension due to its frequency in the hypertensive population.

3.1.2. Risk factors of Essential Hypertension

Many epidemiological studies have identified a wide range of risk factors related to essential hypertension. For example, the following have been found to be predictors of essential hypertension: being over 45 years old of age (Victor, et al, 2008), being male rather than female (Munter, et al., 2011), being African - American rather than Caucasian or

Hispanic (Kato, 2012), and having a genetic predisposition or a family history of hypertension (Victor, et al., 2008; Qi, et al, 2012). In addition, less than 12 years of education, health illiteracy, and low socioeconomic status (less than $16,000 annual house income) have been associated with clinical hypertension (Victor, et al., 2008). Meta-analyses of epidemiological surveys have also presented the following factors as enhancing the risk of clinical hypertension: physical inactivity (Rossi, et al, 2012), short sleep duration (less than five hours per night for those less than 60 years old) (Dean, et al., 2012) as well as body mass index (BMI) over 35kg/m2 , childhood obesity (Park, Falcones, Viner, Sinra, 2012), high birth weight (Mu, et al., 2012), and obesity (Victor, et al., 2008). However, other studies have shown that it is rather waist-to-height ratio than waist-to-circumference which provides better evidence of predisposition to hypertension (Ashwell, Gunn, & Gibson, 2012).

Some levels of dietary and liquid intake have been reported as risk factors for clinical hypertension. Substances which increase the intravascular volume of blood (e.g., nicotine, colas, and caffeine) have been found to predict primary hypertension (Webber, et al, 2012). Poor dietary intake, alcohol consumption (Peters, 2012), and excess of salt intake (Kaplan & Victor, 2010) have been shown to be cardiometabolic factors of essential hypertension. For example, some meta-analyses on consumption of diary foods have reported an inverse association with low-fat diary food, fluid dairy food (e.g., milk and yogurt) and essential hypertension (Ralston, Lee, Truby, Palerno & Walker, 2012). Vitamin D deficiency, diabetes mellitus (DM) and dyslipidemia (Joint National Commission, 2003) have also been found to be risk factors for clinical hypertension. These factors (obesity, smoking, diabetes, and dyslipidemia) have been considered as predictors of atherosclerosis, which in turn, has been

reported as a major factor of essential hypertension (Webber, Sequin, Burnett, Clark, & Otto, 2012).

Some electrolytes related to the kidney such as microalbuminuria (low albumin) or GFR (Glomerular Filtration Rate, to find how well kidney works) <60ml/min (Joint National Commission: JNC, 2003) and lipoprotein-cholesterol (LDL-C) (Worrall-Cartel, et al., 2011) have been reported to be predictors of clinical hypertension. A low level of 24-hour urine excretion of citrate and low levels of potassium, magnesium, calcium, and phosphorous, as well as toxic exposure, air pollution, and lead have been correlated with clinical hypertension (Kaplan & Victor, 2010). Finally, some meta-analyses of prospective cohort studies have found depression to be independent risk factor of clinical hypertension (Meng, Chen, Yang, Zheng, & Hui, 2012).

3.1.3. Prevalence of HTN

3.1.3.1. Prevalence of HTN in the World

Data released by the World Health Organization (WHO) in 2012 from 194 countries show that "one in three adults worldwide," particularly those in "low- and middle-income countries are hypertensive. According to the annual report of the WHO (2012), hypertension is involved in 50% of death related to stroke and heart disease while obesity and body mass index (BMI>30 Kgm2) remain prominent factors in the increase of HTN. The percentage of adults aged 25 years and over with hypertension by WHO region (2008) is reported as follows: Africa 40%, Eastern Mediterranean Region 30%, European Region 29%, Western Pacific Region 26%, South Eastern Asia Region 25%, and Region of Americas 23%. As hypertension increases in the world, the WHO report (2012) indicates that the "world is

getting heavier" (i.e., BMI > 30 Kg/m2). Obesity is found in the following regional percentage: Americas (27%), Europe (23%), Eastern Mediterranean (18%), Africa (8%), Western Pacific (6%), and South Eastern Asia (3%).

3.1.3.2. Prevalence of HTN in USA

According the October 2012 National Center for Health Statistics (NCHS) from the Center for Disease Control and Prevention (CDC) of the U.S Department of Health and Human Services, the prevalence of hypertension among U.S adults aged 18 and over was 28.6% in 2009-2010. In terms of age-adjusted prevalence reported by NCHS (2012), finds hypertension in 6.8% of those between 18-39; 30.4% of those between 40-59; and 66.7% among those 60 and over. In regard to gender, 29.4% of American men and 27.5% of women were hypertensive in 2010. In terms of race and ethnicity, non-Hispanic blacks had a high prevalence of hypertension (40.4%), followed by non-Hispanic White (27.4%), and Hispanic (26.1%) (Yoon, Burt, Luis, & Carroll, 2012).

3.1.4. Pathophysiology of HTN

3.1.4.1. Blood Flow and Hypertension

To understand how the previous risk factors lead to clinical hypertension, it is important to grasp the mechanism of blood flow (i.e., the amount of blood moved per unit of time). In explaining blood flow, McCance and her colleagues (2010) have emphasized that flow is "regulated by the same physical properties that govern movement of simple fluids in a closed, rigid system, that is, pressure, resistance, velocity, turbulent versus laminar flow, and compliance" (p.1117). Pressure in the context of a liquid system is conceptualized as the force exerted on the liquid per unit area and expressed as dynes per square centimeter

(dynes/cm2) and millimeter mercury (mmHg) (McCance, Huether, Brashers, & Rote, 2010). Blood flow is affected by the difference between pressures in the arterial and venous vessels supplying the organ. In terms of movement of fluid, blood flow starts from a region of greater pressure (i.e., arterial side of capillaries) to a region of lesser pressure (i..e, the venous side) (McCance, Huether, Brashers, & Rote, 2010).

In terms of resistance to blood flow, experts have shown the diameter and the length of the blood vessels to be major factors (McCance, Huether, Brashers, & Rote, 2010). For example, any increase or decrease in vessel diameter and opening or closing of vascular channels can cause opposition to blood flow. Therefore, there is an "inverse" relation between resistance and blood flow, where "increased resistance leads to decreased blood pressure" (McCance, Huether, Brashers, & Rote, 2010, p.1118). Blood flow (Q) has been calculated as the measure of pressure at the inflow end of the vessel (P1), pressure at the outflow end of the vessel (P2) and resistance: Q=difference P/R (McCance, Huether, Brashers, & Rote, 2010). Resistance has been reported to be greater in smaller vessels than in larger vessels. McCance and her colleagues have found that flow is inversely affected by the viscosity or thickness of the fluid where thicker fluid moves more slowly and leads to greater resistance than a thin fluid does. In the blood, viscosity is dependent on the volume of red cells (i.e., hematocrit) where a greater amount of red cells in the blood causes greater resistance to blood flow.

Blood velocity (i.e, the distance blood travels in a unit of time: cm/sec) appears to be associated with blood flow. McCance and her colleagues have indicated a direct relation between blood velocity and blood flow but an inverse association between blood velocity and

the cross-sectional area of the vessel in which blood flows. In this sense, narrow arteries lead to quick blood flow. On the other hand, a cross sectional increase in diameter, for example from the aorta to the capillaries, has been known to decrease the velocity of blood (McCance, Huether, Brashers, & Rote, 2010).

Other important factors of blood flow are laminar flow, turbulent flow, and vascular compliance. Experts have indicated that flow through the tubular system can be either laminar (i.e., blood moves "straight ahead" in concentric layers of molecules) or turbulent (i.e., obstruction of blood flow related to vessel turns or rough surfaces). In terms of laminar flow, large vessels are known to have a large center layer and less resistance to flow. These large vessels also have greater flow and velocity than small vessels (McCance, Huether, Brashers, & Rote, 2010). Vascular compliance is an accommodative relation through which an increase in the volume of a vessel is directly associated with an increase in pressure. Elasticity of arteries is very important for the vessel to respond to any increase in pressure due to a large volume of blood. One risk factor to vascular compliance is stiffness. For example, findings have reported that arteriosclerosis as one of the most common causes of an increase of stiffness or rigidity in the arterial walls, which leads to increases of arterial pressure at a given volume of blood (McCance, Huether, Brashers, & Rote, 2010).

Therefore, it could be concluded that changes in the pressure of blood flow (i.e., higher), resistance to blood flow, velocity of blood flow (i.e., faster) as well as turbulent flow, laminar flow, and compliance lead to clinical hypertension. For example, atherosclerosis, dyslipidemia, and LDL-C have been found to cause resistance to blood flow, hindrance to velocity of blood, or causes of vascular compliance, which in turn leads to

cardiovascular problems and clinical hypertension (Webber, Sequin, Burnett, Clark, & Otto, 2012; McCance, Huether, Brashers, & Rote, 2010). While blood flow remains an important mechanism in the pathophysiology of clinical hypertension, the effects of hormones on blood circulation and the regulation of electrolytes are considered to be other pathophysiological mechanisms.

3.1.4.2. Effects of Hormones in HTN

Various hormones have been found to play important roles in hypertension through constriction of vascular beds (e.g., epinephrine, norepinephrine, antidiuretic hormone, renin, angiotensin II, aldosterone, and adrenomedullin). Epinephrine and norepinephrine (NE) are two neurotransmitters which play important roles in the pathogenesis of clinical hypertension. NE is more involved in vasoconstriction, that is, the narrowing of the blood vessels which leads to the contraction of the muscular wall of the vessels in many vascular beds (McCance, Huether, Brashers, & Rote, 2010). Studies have found increased production of catecholamines (e.g., epinephrine and norepinephrine) in individuals with hypertension due to over-activation of the sympathetic nervous system (SNS). The SNS is activated by certain factors (e.g. physical and emotional stress, trauma, anxiety, and burnout), which can increase the heart rate (i.e., number of heartbeats per minute: 70 beats/min in adults) and vasoconstriction (Kaplan & Victor, 2011; McCance, Huether, Brashers, & Rote, 2010).

Another hormone which plays an important role in the pathogenesis of hypertension is the antidiuretic hormone (ADH). Antidiuretics, released at the pituitary, are involved in the reabsorption of water by the kidney, which leads to an increase of blood plasma volume and blood pressure (McCance, Huether, Brashers, & Rote, 2010). McCance and her colleagues

(2010) have reported that this hormone can be affected by obesity and an elevated intake of sodium as well as by a poor dietary intake of potassium, magnesium, and calcium. Dysfunction of these hormones causes salt retention, which leads to hypertension.

Renin, angiotensin, and aldosterone are three hormones from the renin-angiotensin-aldosterone system (RAAS) which play important roles in the regulatory loop and in hypertension. Dysfunction of the RAAS system is considered to be one of the important factors contributing to hypertension. For example, renin is known to control such factors as (a) a drop in blood pressure; (b) decrease of sodium chloride; (c) Beta-adrenergic stimulation (by increasing renin release); (d) angiotensin II (by decreasing renin release); and (e) in lowering potassium concentration in the plasma in order to increase renin release (McCance, Huether, Brashers, & Rote, 2010). Another important hormone in the pathogenesis of hypertension is angiotensin II (Ang II). Ang II is the conversion of Ang I (i.e., created when renin splits off a polypeptide from angiotensinogen) by the angiotensin-converting enzyme (ACE). The involvement of this hormone is mostly seen in the stimulation of thirst, the release of antidiuretic hormone, and in the increase of the sympathetic nervous system output (McCance, Huether, Brashers, & Rote, 2010). The last hormone of the RAAS system which is involved in the pathogenesis of hypertension is aldosterone. This hormone is released by the adrenal cortex after the effect of the Ang II. The deleterious effects of aldosterone (e.g., increased production of toxic oxygen radicals) have been associated with the overproduction of urine, which in turns leads to decrease of blood volume and blood pressure (McCance, Huether, Brashers, & Rote, 2010).

Finally, adrenomedullin (ADM) is a peptide which is involved in natriuretic properties and has vasodilatory effects (i.e., increase of the internal diameter of blood vessels due to relaxation of its muscle) affecting blood flow. Changes in ADM have been associated with cardiovascular and renal disease, cancer, and hypertension. McCance and her colleagues (2010) have reported an association between inflammation, endothelial dysfunction, obesity related- hormones, and insulin resistance, on the one hand, with hypertension.

3.2. Deleterious Impact of Hypertension on the Heart, the Kidney, and the Brain

Various risk factors of HTN have been linked to the pathogenesis of systolic and diastolic hypertension, which in turn has been associated with various complications (e.g., arterial diseases, organ damage, silent vascular cognitive impairment, and death) (Kaplan & Victor, 2010). Kaplan and Victor (2010) have reported that untreated clinical hypertension is involved with structural changes in the resistance of arterioles such as vascular remodeling (i.e., the active process through which the blood vessel changes its geometry) and hypertrophy (i.e., an increase in the volume of a tissue or organ). These structural changes have been understood to play an important role in the pathogenesis of small-vessel arteriosclerosis (i.e., the loss of elasticity or thickening and hardening of arteries), which is associated with organ damage (Kaplan & Victor, 2010). In addition, Laka and Levy (2003) have indicated that large-artery arteriosclerosis, which is enhanced by hypertension, has been involved in different processes: lipid disturbances, platelet activation, thrombosis, endothelial dysfunction, inflammation, oxidase stress, vascular smooth cell activation, altered matrix metabolism, and remodeling.

3.2.1. HTN and Arterial Lesions

Kaplan and Victor (2010) have reported the following vascular lesions as common types of arterial lesions related to hypertension: (a) fibrinoid necrosis (i.e., tissue death due to the accumulation of amorphous proteinaceous material in the tissue); (b) hyaline arteriolar sclerosis (i.e., the thickening of the walls of arterioles by the deposition of hyaline material); (c) miliary aneurisms in small penetration arterioles, which lead to cerebral hemorrhage; (d) artherosclerotic plaques in the areas of thrombi, which will be involved in ischemia and infarction in the heart, kidney, and brain; (e) medial damage in the wall of the aorta, which causes plaque, aneurism, and aortic dissections; and (f) hyperplastic arteriolar sclerosis. In the context of hypertension, atherosclerosis has been considered as the condition in which an artery wall thickens as result of the deposit of fatty material such as cholesterol, triglyceride, low density of LDL, and plasma proteins (Kaplan & Victor, 2010).

3.2.2. HTN and Organ Damage

Hypertension has been found to have a deleterious involvement with organs such as the heart, the kidney, and the brain. Epidemiological evidence has found that hypertension is highly correlated with heart diseases (e.g., coronary disease, acute myocardial infarction, sudden death, congestive heart failure, left ventricular hypertrophy, myocardial ischemia and infarction, coronary heart disease, atrial fibrillation, and aortic stenosis) (Kaplan & Victor, 2010). For example, 90 % of severe systolic hypertension is related to left ventricular hypertrophy (LVF), two thirds of diastolic hypertension in individuals over 65 years old leads to congestive heart failure (CHF) while 32% of HTN lead to aortic stenosis (Kaplan & Victor, 2010). In addition, hypertension has been shown to be a leading cause of large-vessel diseases. Systolic readings higher than 195 mm Hg have been associated with

abdominal aortic aneurism (AAA) while 80% of aortic dissection is caused by HTN. Finally, hypertension has been associated with peripheral vascular disease (Selvin & Erlinger, 2004), takayasu arteritis (Weaver et al., 2004), and carotid artery disease (Parti et al., 2008).

Hypertension is involved in various kidney diseases (e.,g., chronic kidney disease and end-stage renal disease) through the activation of RAAS. However, the relation between hypertension and renal disease is a two-way street, where HTN leads to chronic kidney disease and chronic kidney disease leads to HTN (Kaplan & Vitor, 2010). Risk factors such as an increase in salt intake, low potassium, and low magnesium in hypertensives have been found to be predictors of symptoms such as proteinuria (i.e., the presence of protein in urine), decreased glomerular filtration rate (GFR) (Kaplan & Victor, 2010), microalbuminuria (Danzinger, 2008 cited by Kaplan & Victor, 2010), and serum cystain (i.e., a protein filtered by glomerulus). These imbalances of electrolytes associated with hypertension are considered to be cardiovascular risk factors in acute kidney disease, chronic kidney disease, or end-stage renal disease (Zoccali, Mallamaci, & Tripepi, 2002).

Hypertension has been found to play a more important role in silent cerebrovascular disease (CVD) than in heart disease (Kaplan & Victor, 2010) and in other brain lesions. Stroke (CVD) is the second leading cause of mortality in the world and contributes to neurological disability, hospitalization, and long-lasting care (Donnan, et al., 2008). The WHO 2012 report has indicated that hypertension (i.e., blood pressure above 130/80 mm/Hg) is involved with 50% of strokes. Studies have found that 80% of strokes caused by hypertension are related to arterial thrombosis or embolism and 15% are intraparenchymal hemorrhages while 5% are subarachnoid hemorrhage (Kaplan & Vitor, 2010). To underline

the pervasive character of HTN, researchers have reported that individuals with HTN have a 2.7 times greater incidence of strokes and brain lesions than normotensive (Qureshi, et al., 2002). Finally, hypertension has been associated with lacunar infarction from small vessel lesions and lacunar stroke (Lammie, 2000).

3.2.3. Physiological and Neuroanatomical Impacts of HTN on the Brain

Hypertension has been associated with many vascular changes in large and small vessel lesions which lead to physiological, neuroanatomical, and metabolic changes. Raz and Rodrigue (2003) have found the presence and progression of white matter abnormalities in individuals with hypertension. Although white matter lesions (WML) have been related to normal aging processes, Sierra and Coca (2006) have reported an increasing prevalence of WML (44%) among hypertensive people over 65 years old compared with 33.3% in normotensive of the same cohort. White matter lesions in HTN have been associated with the presence of arteriolosclerosis (i.e., the thickening of the walls of arterioles by the deposition of hyaline material). Studies have considered WML to be the primary stage of brain dysfunction in hypertension.

Brain atrophy has been found in individuals with hypertension mostly in structures such as the frontal, temporal, and occipital lobes (Gold, et al., 2005; Den Heijer, et al, 2004; Raz & Rodrigue, 2003). In addition, brain atrophy was found in the hippocampus, amygdala, anterior cingulate, and thalamus (Du AT, et al, 2006; Den Heijer, et al, 2005). For example, den Heijer and his colleagues (2005) have found that individuals with higher diastolic hypertension had reduced hippocampus volume while low diastolic participants had more severe atrophy. This study has also shown that hypertensives with WML had severe atrophy

in both hippocampus and amygdala. Other studies have correlated brain atrophy in hypertensive individuals with the dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis (Gold, et al., 2005). The over-activation of CNS in individuals with hypertension has been found to impair their glucocorticoid feedback. The elevation of cortisol level has been related to the atrophy in the hippocampal volume and in the frontal lobe (Gold, et al., 2005). Finally, de Heijer and his colleagues (2005) also found neurofibrillary tangles and amyloid plaques in small vessels of the hippocampus in participants with hypertension.

Various brain mechanisms and physiological processes in the brain are impacted by hypertension. Summarizing research on the impact of high BP on neurocognition, Gunstad and colleagues (2010) have listed the following brain changes in hypertensive brains: disruption in the blood-brain barrier function, reduction of functional neuroconnectivity, vascular remodeling and impaired autoregulation as well as higher oxidative stress and/or systemic inflammation, cerebral microbleeds, and amyloid angiopathy (i.e., neurological condition where proteins build up in the wall of the arteries in the brain). Jennings (2003) has found reduced regional blood flood (rCBF) in the lateral prefrontal (Broca's area)/ insula, the amygdala and the hippocampus. Gianaros and his colleagues (2006) have reported higher systolic HTN to be a predictor of decreased grey matter volume in the superior frontal gyrus, the right anterior cingulate cortex, the left middle temporal gyrus, and the supplementary motor area. Researchers have reported that hypertension leads to vascular changes, interruption of blood flow, and changes in metabolism. Finally, hypertension is involved in neurophysiological changes (i.e., arteriolosclerosis) which may predispose either to occlusion, complete infarct, lacune, and lacunar state or with hypoperfusion, incomplete

infarct, white matter signal hyperintensities, neuroanatomical changes, and vascular dementia (Reman, Erkinjunti, Wallin, Pantoni, & Chui, 2002).

In summary, wide ranges of studies have suggested pathophysiological mechanisms for HTN and the deleterious impact of HTN on major organs (e.g., the heart, kidney, and brain). Related to the brain, hypertension is associated with atherosclerosis leading to small and large vessel diseases, brain atrophy, and structural changes causing microvascular diseases, the reduction of blood flow, and dysfunction in the cerebral metabolism. Other potential mechanisms related to hypertension include changes in different autoregulatory processes, alterations in brain neurochemistry, changes in cellular function in the brain, and an increase in cardiovascular or neuroendocrine reactivity (Waldstein, 1995). These neuropathological changes in individuals with hypertension are known to lead to the trajectory of dementia of Alzheimer's Disease, vascular dementia, and vascular cognitive impairment.

3.3. Relation of HTN to Dementia, Vascular Dementia, and Vascular Cognitive Impairment

Various physiological changes in the brain related to HTN have been associated with a pattern of dementia in Alzheimer's Disease (AD), vascular dementia (VaD), and deficits in neuropsychological tests in different cognitive functions. Many meta-analyses have found that hypertension led to structural changes and brain atrophy (e.g., the hippocampus and cortex), neuritic plaques, formation of tau proteins or neurofribillary tangles, beta-amyloid peptides, white matter lesions, and cerebral vascular lesions. These changes have been reported in the pathogenesis of neurodegenerative diseases (e.g., Alzheimer's Disease, Parkinson's Disease, Lewy Body disease) and in the dementia associated with these diseases

(Joas, et al., 2013; Power, et al., 2011; Novak & Hajjar, 2010; Duron & Hanon, 2008). In addition, hypertension has been found to have direct and indirect correlations with vascular dementia (e.g., multi-infarct dementia, strategic infarctual dementia, and small-vessel disease). Several review articles and meta-analyses have noted a positive relation between hypertension and incidents of vascular dementia (Joas, et al., 2013; Launer, et al., 2010; Duron & Hanon, 2008). Finally, a wide range of studies has shown that hypertension may contribute to a "slowly progressive course" of vascular cognitive decline (Cherubini, et al., 2010).

3.3.1. Predictors of the Correlation between Hypertension and Cognitive Function

Meta-analyses and various studies have presented conflicting findings (Duron & Hanon, 2008) and equivocal relationship between hypertension and dementia, VaD, and vascular cognitive impairment (Power, et al., 2011; Novak & Hajjar, 2010). On one hand, the ambiguity of the relation between HTN and dementia or cognitive decline could be explained by the complex interaction between the potential mechanisms of action of HTN in the brain and their neuropsychological expression (Power, et al., 2011). On the other hand, the conflicting findings about the association between hypertension either with dementias or vascular cognitive impairments have been related to the following confounding factors: chronological onset, duration of hypertension, type of hypertension (e.g., SBP and DBP), treated or untreated hypertension, controlled or uncontrolled hypertension, the design of the study, and type of cognitive function tested. These potential factors will now be reviewed.

3.3.1.1. Effect of Chronological Onset on the Relationship between Hypertension and Cognitive Function

Hypertension-dementia and cognitive functions have been understood as related in the context of chronological onset. Some epidemiological studies have found that untreated midlife hypertension (i.e., between the ages of 50 and 60) was likely to be a predictor of dementia or cognitive decline in late life (Joas, et al., 2012, Launer, et al., 2011, Novak & Hajjar, 2010, Knetch, et al., 2009, Tsivgoulis, et al,. 2009; Duron & Hanon, 2008; Qiu, Winblad, & Fratiglioni, 2005; Singh-Manoux & Marnot, 2005; Korf, White, Scheltens, & Launer, 2004). For example, some neuroimaging studies have identified some Alzheimer's disease biomarkers, such as atrophy of the hippocampus, white matter lesions, neuritic plaques in middle hypertensive participants who did not take an antihypertensive (Power, et al., 2011). Novak (2012) has suggested that cerebral hemodynamics failure (i.e., blood flow movement) during the midlife can be considered as a predictor of cognitive deficits. However, other review articles have reported that midlife hypertension was less likely to increase risk of dementia (Power, et al., 2011). A number of researchers have found late life hypertension to be associated with dementia or cognitive impairment (Bermejo-Pareja, et al., 2010; Peters, et al., 2006, 2008, 2009; Vinyoles, et al., 2006; Reitz, et al., 2007; Hayden, et al., 2006; Li, et al., 2001).

Reporting on the relationship of hypertension to neuropsychological performance from a lifespan perspective, Waldstein (2003, 1995) has found deficits in various cognitive functions (e.g., learning and memory, attention span, executive function, speed of information processing, and visuoconstructional abilities) in both young to middle-aged (i.e, 20-60 years old) and older (i.e, 60 years and older) individuals with hypertension. Although there were deficits in both groups, Waldstein (1995) has noted greater severity of impairment

of some cognitive functions (e.g., learning and memory, attention, and executive functions) in older hypertensives. Some studies have also investigated individuals who have family histories of hypertension. The studies have found that the offspring of hypertensives who themselves also developed hypertension, had more cognitive decline than children of normotensive parents (Pierce & Elias, 1993; Waldstein, et al., 1994).

3.3.1.2. Duration of Hypertension and Relationship between Hypertension and Cognitive Function

The conflicting findings on the association between hypertension and cognitive decline or dementia have been explained by the slow progression of HTN or the duration of hypertension. Researchers have found that the effect of hypertension on cognitive function and dementia depends on the duration of individual's hypertension (Birns & Kalra, 2009). For example, assessing hypertensive individuals aged between 59-71 during four years, Tzourio and colleagues (1999) found an inverse correlation between the duration of hypertension and cognitive performance. Other investigations have reported that the duration of hypertension can have a deleterious effect on cognitive functions only after duration of more than 10 years (Waldstein, 1995, 2003).

3.3.1.3. Types of Hypertension and the Relationship between Hypertension and Cognitive Function

An increase or decrease of systolic blood pressure (SBP) and diastolic blood pressure (DBP) has been associated with vascular cognitive impairment or dementia. In order to understand the impact of types of hypertension on cognitive function, it is important to show the type of hypertension which affects the brain over various stages of one's lifespan.

Epidemiological studies have reported that systolic hypertension was more prevalent in young adults (17-25 years) while high diastolic blood pressure with systolic either normal (isolated diastolic hypertension) or both high SBP and DBP were frequent in middle age (35-50 years). In addition, isolated systolic hypertension (BP >140 mm Hg and diastolic <90 mm Hg) was often reported in older adults (50 years and older) (Kaplan & Victor, 2010). These variations of HTN in the different stages of life are associated with cognitive decline. For example, some studies have found a negative correlation between cognitive performance and SBP (Kuo, et al., 2004; Seux, et al, 1998; Kilander, et al., 1998). Yamada and colleagues (2003) found incidences of vascular dementia in individuals with SBP. Other investigators have reported poorer cognitive performance in patients with high DBP. While some studies have found negative correlations between cognitive function and DBP (Gale, et al., 1996), others have reported a positive association between DBP and cognitive performance (Reinprecht et al., 2003; Cacciatore et al., 1997). Power and colleagues (2011) have noted that mid-life diastolic blood pressure may contribute to AD more than systolic hypertension. These researchers found that increases of late-life blood pressure were beneficial to older individuals. Contrary to previous findings, many cross-sectional and longitudinal studies have found significant cognitive impairments in patients with both high SBD and DBP (Kuo, et al., 2005; Elias et al., 2003; Knopman et al., 2001; Tzourio et al., 1999; Starr, et al., 1993; Elias et al., 1990). Incidences of vascular dementia (Launer et al., 2000), dementia of AD (Wu et al., 2003, Kivipelto et al., 2001; Morris et al., 2001; Launer, 2000), and undifferentiated dementia (Whitner at al., 2005) have been found in longitudinal studies in individuals with both high SBP and DBP. Finally, investigations have also found that a

drop in systolic or diastolic blood pressure (i.e, orthostatic hypotension) to be associated with poor cognitive performance (Novak, 2012; Novak & Hajjar, 2010).

3.3.1.4. Study Design and the Relationship between Hypertension and Cognitive Function

The design selected for studies of hypertension and cognitive function or dementia has been been found to influence the findings. Many meta-analyses have classified such studies on the effect of HTN according to their research designs (e.g., longitudinal or cross-sectional design) (Birns & Kalra, 2009; Duron & Hanon, 2008). Birns and Kalra (2009) reviewing 28 cross- sectional studies between 1985 and 2005 noted incompatible results. In this same review, 23 studies found significant associations between hypertension and cognitive deficits while five other investigations did not report this same association. In terms of the directionality of the relationship of hypertension and cognitive function, the results of cross-sectional studies presented positive and negative correlations and various shapes of correlations (Birns & Karla, 2009). In addition, exploring 22 studies on the hypertension-cognitive function relation done between 1995 until 2004, Birns and Kalra (2009) found in all the studies that hypertension was correlated with poor cognitive performance. This meta-analysis, however, suggested that longitudinal studies report mostly negative or inverse correlations (14 out of 22 studies), but also clustered positive correlations (3 out of 22 studies), U-shaped correlations (2 out of 22 studies), quadratic correlations (i. e., a correlation where the coefficient is zero), and J-shaped correlations (Birns & Kalra, 2009).

These findings could suggest that the significance and the directionality of the correlation between HTN and cognitive performance may be dependent on the study design. In addition, reviews examining these cross-sectional or longitudinal studies have reported

limitations with sample size, power, and the psychometric properties of the tests used. Some of these studies have found that hypertension had an impact on some cognitive domains rather than others. These results will now be described.

3.3.2. Hypertension and Various Cognitive Functions

The types of cognitive function assessed in studies of the association between hypertension and cognitive performance have been found to affect the findings. For example, previous studies have found that hypertension was a predictor of poor neuropsychological performance in general intelligence, executive functions, learning and memory, attention, speed of information, processing, visual spatial skills, and psychomotor abilities (Waldstein, 1995, 2003).

3.3.2.1. HTN and General Intelligence

Hypertension is related to deficits in some abilities of general intelligence. Horn (1975) has divided general intelligence into crystalized intelligence (i.e., overlearned abilities which depend on the education and culture) and fluid intelligence (i. e, related to solving novel problems based on speed and abstraction). Wechsler Intelligence Scales (e.g., WAIS, WAIS-R, WAIS-IV, and WASI) have been commonly selected to assess general intelligence. Studies have reported conflicting results on the relation between hypertension and general intelligence, with some researchers reporting poor performance in general intelligence, which others did not report (Waldstein, 2003). In addition, some studies have noted a negative correlation between hypertension and both crystalized and fluid intelligence abilities (Waldstein, 1995). However, others have only reported deficits either in crystalized intelligence (Wilkie & Eisdorfer, 1971) or in fluid intelligence (Elias, et al, 2004). Some

longitudinal studies over 20 years examining age differences in cognitive decline using the WAIS have found that high SBP and DBP were predictors of a deficit in fluid abilities in both younger age groups (18 to 46 years old) and older age groups (47 to 83 years old) (Elias, et al., 2004). Knowing that hypertension affects frontal and parietal lobes, these findings may be consistent with other neuroimaging studies which have also found the prefrontal and parietal regions to be possible brain areas involved in fluid intelligence (Gray, Chabris, & Braver, 2003; Duncan, Burges, & Emslie, 1995). Fluid intelligence is known to be closely related to executive functions. In terms of statistical power, Waldstein and colleagues (1991) reported a small ES (0.27) of HTN on Wechsler subtests and more than a medium ES (d=0.63) for HTN on the Picture Arrangement subtest.

3.3.2.2. HTN and Executive Functions

Executive functions (EFs) have been one of the cognitive functions assessed in studying the correlation hypertension-cognitive function (see Table 6). In this table, studies are summarized by their sample size, gender, average age of the participants, measure used, means of SBP/DBP, and by their findings. Using the Lezak model of EFs (1995) and referring to the tests used by previous studies, the following components of EFs were examined: planning, purposive action, and self-regulation.

Table 6: Studies assessing the Relationship of HTN and executive functions.

Authors and year	N	Gender	Mean/SD age	Measure Used	Mean/SD SBP	Mean/SD DBP	Findings
Kilander, et al., 2011	Treated/untreated 998 240 240		50-70 yrs	MMSE -33(0.82) TMT B		>105 mm Hg	Cross-sectional analyses show inverse relationship between HTN and cognitive function (EF) mostly in untreated men.
Vasilopoulos, et al., 2012	1237 Control group Untreated Treated		55.4 yrs	Stroop Verbal Fluency TMT A & B DKFES			No significant association between 3 groups of BP and performance in EFs.
Vicario, et al., 2011	60 Under meds	65% female	65-80 yrs under med HTN 72.5 SD=4.2	TMT A TMT B Clock drawing Stroop (Color & word)	141.4 SD=17.8	80.8 SD= 9.02	Poor cognitive performance in measures of EF regardless the adequacy of HTN drugs and HTN values.
Oveisgharam, et al., 2010	990	Men= 51%	83.06 SD=6.97	FAS Test BVRT Digit Symbol of WAIS-R			Relation of HTN with progression to dementia in older individuals with executive dysfunction.
Bucur, & Madden,, 2010	134 Controlled 71 Chronic BP=63		19-39 yrs=47 41-58 yrs=44 60-79 yrs= 43	Verbal Fluency Stroop interf. Digit sym cod			Association between a differential decline in HTN and EFs.

Knecht, et., 2009	377	Male=171 Female= 206	64 SD=6.62	DSST TMT A & B Category and letter fluency	144 SD=18.79	84 SD=10.76	Inverse relation between SBP with cognitive performance (EF).
Elias, et al, 2004	529		46	Stroop interf.			Significant decline in fluid abilities in subjects with HTN.
Waldstein, et al., 2005	847	Male=503 and Female = 344	70.6 SD=8.5	TMT A & B Letter fluency Category Fluency	138.7 SD=20	82 SD=10.9	Both SBP and DBP associated with poor performance in EF measures.
Saxby et al., 2003	506 hypertensives and normotensive,223 untreated.	.		TMT A& B	164 SD=9	89 SD=7	Poor performance in EF measures in hypertensive group.
Vicario, et al., 2005	60 meds controlled Uncontrolled Control group		65-80	Stroop Color Words, TMT B Alternating series Test Test of drawing copy			Deficits in measures of EF (TMT B and Stroop Color and Word) in
Brady, et al., 2005	357 Control group Controlled Uncontrolled		67	Category Fluency (animal)			Uncontrolled HTN was associated with EF deficit in older subjects, which cannot be attributable to age.

These studies have reported an inverse association between hypertension and these components of EFs. However, these findings are not always consistent. For example, Wolf and colleagues (2007) have reported deficits on tests of executive functions (e.g., TMT B) in individuals with hypertension. Using Trail Making Condition 4 and Verbal Fluency Category Switching, Vasilopoulos and colleagues (2012) did not find a significant correlation between midlife individuals with hypertension (treated and untreated) and EFs. In addition, their study did not report any significant difference in EFs between normotensive and treated or untreated hypertensives.

Executive functions have been found to be one of the cognitive functions the most impaired by hypertension. Waldstein and colleagues (1991) found a large ES (d=0.89) of hypertension on three measures of abstract reasoning. These same authors have reported a medium ES (d=0.48) of hypertension on the measure of Category Test and Card Sorting (d=0.45) while other studies found a small ES (0.26). Calculation of the size effect by using the Cohen's d statistic (i.e., 0.2 to 0.3 is considered as small; 0.5 as medium; and 0.8 to infinity as large) has suggested a range of effect size of hypertension on EFs which varies between small to large. The severity of the impairment can be calculated by using the effect size (i.e., the statistical difference between the means of the treatment group and the means of the control population divided by standard deviation): (1.0)

$$ES_{ai} = \frac{\mu_1 - \mu_2}{\sigma}$$

In calculating the SD, Lipsey (1990) has suggested two possibilities: (1) when the sample size of the treatment (nt) and control (nc) are different, then the common standard deviation

to be used in ES is the pooled standard deviation (Sp) (i.e., variances for treatment and control group respectively), which can be calculated: (2.1)

$$S_p = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{(n_1 - 1) + (n_2 - 1)}}$$

(2) when the sample size of the treatment and the control group are the same (nt = nc), the pooled standard deviation is calculated:

$$S_p = \sqrt{\frac{s_1^2 + s_2^2}{2}}$$

For example, comparing EFs in 107 hypertensive and 116 normotensive older adults who were assessed with Trail Making Test A & B, Saxby and colleagues (2003) found significant negative association between hypertension and executive function (Mt=148, SD=297; Mc=263, SD=269, p. < .01). After calculation using formulas (2.1) and (1.0), a medium effect size (0.41) was found. In addition, Vicario and colleagues (2005) using 30 normotensive and 60 hypertensives with Stroop Color and Word found also a significant inverse correlation between hypertension and EFs (Mt=24.7, Sd=7.6; Mc=32.7, Sd+10.7). These results suggest a large ES (0.92) of hypertension on EFs. However, Van den Berg and colleagues (2009) have also found smaller effect size (0.1) of hypertension on measures of executive functions (e.g., verbal fluency and abstract reasoning).

Vulnerability of some brain regions in individuals with hypertension has been associated with poor neuropsychological performance in executive functions. For example, neuroimaging studies have found that a smaller prefrontal cortex (Gold, et al., 2005; Raz, Rodrigue, & Acker, 2003), white matter lesions (O'Brien, et al., 2002; Prins, et al., 2005),

increased white matter hyperintensities (Raz, Rodrigue, & Acker, 2003), and a hypersensitive hypothalamo-pituitary-adrenal axis (HPA) (Gold, et al, 2005) to be predictive of poor executive functions in individuals with hypertension. These findings are consistent with neuroimaging studies which have noted the major role of the prefrontal cortex and white matter pathways in EFs (Bowirrat, et al., 2012; Callahan, 2009).

3.3.2.3. HTN and Attention

Some components of attention have been found to be impaired by hypertension. Previous studies have examined the four components of attention of Mirsky's model (1991): selective attention, divided attention (Knecht, et al., 2007; Waldstein, 2005; Kilander, et al., 1997); shifting attention (Shehab & Abdulle, 2011), and sustained attention (O'Brien, et all., 2002). Some of these studies have reported a significant negative correlation between hypertension and attention (Shehab & Abdulle, 2011) while others did not find hypertension to significantly impair attention (Vicario, et al., 2011; Saxby, et al., 2003) (See Table 7).

Table 7: Studies Assessing Relationship between HTN and Attention.

Authors	N	Mean/SD age	Measure Used	Mean/SD SBP	Mean/SD DBP	Findings
Shehab & Abdulle, 2011	Total=69 Normal=20 HTN=30 WCH=19	38.2SD=10.8	Shifting attention: PASAT	155 SD =16		White coat HTN was associated with poor shifting attention.
Kilander, et al., 1998	999 Treated not treated	50-70 yrs	Selective and divided attention: TMT A & B		>105 mm Hg	Stronger association between untreated individuals with measure of attention.
Vasilopoulos, et al., 2012	1237	55.4 yrs	Selective and divided attention: TMT B			No significant difference between groups of BP (No, meds, unmeds) and measure of attention.
Vicario, et al., 2011	60 treated	72.5 SD=4.2	Selective and divided attention: TMT B	141.4 SD=17.8	80.8 SD=9.02	No association between HTN and measure of attention.
Knecht, et., 2009	377	64 SD=6.62	Selective and divided attention: TMT B	144 SD=18.79	84 SD=10.76	Linear relation of SBP with measure of attention.
Waldstein, et al., 2005	733	70.6 SD=8.5	TMT A & B	138.7 SD=20	82 SD=10.9	Both SBP and DBP were associated with poor performance in measure of attention.

Saxby et al., 2003	223: 107 untreat. 116 normotens.		Selective and divided attention: TMT B	164 SD=9	89 SD=7	No significant difference between hypertensive and normotensive in measure of attention.
Vicario, et al., 2005	60 Meds	65-80	Selective and divided attention: TMT B			Significant difference between hypertensive and normotensive in measure of attention but no significant difference between controlled and uncontrolled HTN.

Using the Trail Making Test B, Stroop Color-Word, Digit Span, and Digit Backward, researchers have noted a decline of attention in the performance of individuals with hypertension (Elias, et al., 1990; Sands & Meredith, 1992). Other researchers have reported a relation between hypertension and poor performance in TMT B only in hypertensive individuals with 12 to 15 years of education (Elias, et al., Elias, 1987).

Some studies have reported an effect size of hypertension on attention which varies between small to more than medium. For example, Waldstein and colleagues (1991) reported a medium ES (d=0.50) of HTN on Digit Span and on measures of visual attention (ES, d=0.45) and a very small ES on TMT B. Calculating the ES using formulas (2.1) and (1.0), one found no effect size (0) from Saxby and colleagues' study (2003). There is a more than a medium effect (0.6) from Vicario and colleagues' study (2011). These conflicting results on the relation between hypertension and attention may be attributed to the use of less sensitive neuropsychological measures of attention.

Concerning brain regions and attention, some neuroimaging findings have reported consistent associations between brain regions and attention decline in hypertensives. For example, O'Brien and colleagues (2002) found that subcortical gray matter and fiber tract lesions were associated with poor performance in sustained and focused attention in individuals with hypertension. In addition, Van Swieten and colleagues (1991) found that hypertensives with white matter diseases performed poorly in Stroop and TMT B.

3.3.2.4. HTN and Memory

Poor performance in various memory aspects has been found in individuals with hypertension. For example, working memory, immediate memory, short-term memory, and

other aspects of long-term memory (e.g., verbal and spatial aspects of semantic memory) have been found to be impaired in hypertensives (See Table 8).

Table 8: Studies Assessing the Relationship Between HTN and Memory.

Authors	N	Male/ Female	Mean/SD age	Measure Used	Mean /SD SBP	Mean/ SD DBP	Findings
Shehab & Abdulle, 2011	69	Male = 50.9	38.2 SD=10.8	CANTAB-SRMT	155 SD=16		White coat hypertension performed poorly in memory measures.
Kilander, et al., 2011	Treated/untreated 998 240 240		50-70 yrs	MMSE -33(0.82)		>105 mm Hg	Cross-sectional analyses show inverse relationship between HTN and cognitive function (memory) mostly in untreated men.
Vasilopoulos, et al., 2012	1237 Control group Untreated Treated		55.4 yrs	Episodic memory: Logical Memory and Visual Reproduction of WMS, 1997. Short Term Memory: Digit Span Forward and Spatial Span Forward; Working Memory: Digit Span Backward, Spatial Span Backward and Letter-Number Sequencing, WAIS, 1997.			No significant association between 3 groups of BP and performance in episodic memory, short term memory, and working memory.
Vicario, et al., 2011	60 Under meds	65% female	65-80 yrs under med HTN 72.5 SD=4.2	MMSE and New York University Paragraph Test	141.4 SD=17.8	80.8 SD= 9.02	No significant changes in the basal short-term memory and long-term memory in subjects with HTN.
Oveisgharam, et al., 2010	990	Men= 51%	83.06 SD=6.97	Information subtests of WMS, Rey Auditory Verbal Learning Test; Benton Visual Retention			HTN predicted progression to dementia but not in individuals with memory

				Test, Buschke Cued Recall Procedure.			dysfunction.
Knecht, et., 2009	377	Male=171 Female = 206	64 SD=6.62	Auditory Verbal Learning Test (AVLT) for STM, LTM, retrieval, and recognition; Digit Span (WMS-R); Rey-Osterrieth Complex Figure Test (RCFT).	144 SD=18.79	84 SD=10.76	Inverse relation between SBP with cognitive performance (memory).
Elias, et al, 2004	529		46	Arithmetics, Digit Span Forward and Digit Span Backward.			No significant relation of memory in subjects with HTN.
Waldstein, et al., 2005	847	Male=503 and Female = 344	70.6 SD=8.5	Working memory=Digits Forward and Backwards of WAIS; Learning and memory= The California Verbal Learning Test; and Benton Visual Retention Test (BVRT).	138.7 SD=20	82 SD=10.9	Relation between higher SBP and nonverbal memory in nondrinkers; higher DBP and working memory in less educated.
Saxby et al., 2003	506 hypertensives and normotensive,223 untreated.	.		CDR computerized assessment battery on laptop: immediate word Recall, recognition, spatial memory; delayed recall and recognition, numeric working memory, and picture recognition.	164 SD=9	89 SD=7	Poor performance in episodic and working memory measures in hypertensive group.
Vicario, et al., 2005	60 meds controlled Uncontrolled Control group		65-80	MMSE and New York University Paragraph Test			Deficits in measures of immediate/short term memory and delayed recall.

Brady, et al., 2005	357 nondemented Control group Controlled Uncontrolled		67	Digit Span Backward from WAIS-R; Word List Learning Test from CERAD battery.			Uncontrolled HTN was associated with retrieval and immediate recall memory deficit in older subjects.
Insel, et al., 2005	2859 divided between SBP and DBP.		65 years and older	MMSE -33(0.82)	133.63 SD=15.87		Baseline SBP and MMSE did not predict change in MMSE over 7 years in older Mexican Americans.
Elias, et al., 1995	1695	male=688 and Female =1007		Kaplan-Albert Neuropsychological Test Battery.	131.1 SD=17.6	82.1 SD=9.4	Blood pressures and chronicity of HTN were negatively related with visual and verbal memory.

However, assessing episodic memory with the Wechsler Memory Scale (Wechsler, 1997), Short Term Memory and Working Memory with Digit Span Forward and Backward, Vasilopoulos and colleagues (2012) did not find a significant correlation between midlife hypertension and memory. In addition, their study did not report any significant difference in these memory components between normotensive and hypertensive, treated and untreated hypertensives.

An estimation of ES of hypertension on these different memory components has been ranged from medium to large. For example, Waldstein and colleagues (1991) noted a large ES (d=0.80) of HTN on measures of memory, a medium ES (0.56) on measures of recall of a story paragraph, and a small ES (d=0. 21) on tests of verbal associative learning. However, a large effect size (0.96) was reported in a sample of unaware and untreated individuals with hypertension on measures of memory. Van den Berg and colleagues (2009) have also found a medium effect size (0.4) of hypertension over some memory components. Calculating the ES using formulas (2.1) and (1.0), one finds a medium ES (0.53) of hypertension on working memory and on episodic memory (0.46) from Saxby and colleagues' study (2003). Vicario and colleagues' study (2005) found a medium ES (0.54) of hypertension on delayed memory but a small ES (0.30) of hypertension on immediate memory.

Neuropsychological deficits in memory have been correlated with pathophysiologic effects of hypertension on memory substrates. For example, atrophy of structures of the temporal lobe (Den Heijer, et al., 2005), atrophy of the prefrontal cortex (PFC), atrophy lower regional grey matter (Gianaros, 2006), and the presence of white matter lesions (Prins, et al., 2005, O'Brien, et al., 2002) and of neuritic plaques and neurofibrillary tangles (Power,

et al., 2011) have been suggested as predictors of poor memory performance in individuals with hypertension. These neuroimaging findings appeared to be consistent with previous studies which have reported the involvement of these structures in memory functions (Kolb & Whishaw, 2009).

3.3.2.5. HTN and the Speed of Information Processing

Poor speed of information processing has been observed in individuals with hypertension. A number of researchers have reported a significant negative correlation between hypertension and the speed of information processing (See Table 9).

Table 9: Studies assessing Relationship between HTN and the Speed of Information Processing.

Authors	N	Male/ Female	Mean/ SD age	Measure Used	Mean/SD SBP	Mean/SD DBP	Findings
Shehab & Abdulle, 2011	Total=69 Normal=20 HTN=30 WCH=19	Male= 50.7 Female = 49.3	38.2 SD= 10.8	Reaction Time 11 (RT 11)	155 SD=16		Slower reaction time in individuals with white coat HTN.
Vasilopoulos, et al., 2012	1237		55.4 yrs	TMT A & B Stroop (color & Word)			No significant association between different groups of BP (Non, meds, unmeds) and processing speed.
Bucur & Madden, 2010	134			TMT A & B, Computerized Digit symbol Coding task; Stroop task			Age related decline in measures of processing speed in HTN.
Knecht, et., 2009	377	Male= 171 Female = 206	64 SD= 6.62	TMT A & B	144 SD=18.79	144 SD=18.79	High SBP associated with slower processing speed.
Waldstein, et al., 2005	733	Male= 59%	70.6 SD= 8.5	TMT A & B	138.7 SD=20	82 SD=10.9	Both high SBP and DBP were related with poor performance in measures of perceptuo-motor speed among untreated subjects.
Elias, et al, 2004	529		46	Digit Symbol Substitution of WAIS			No significant association between HTN and speed abilities.

Saxby et al., 2003	506 hypertensives and normotensive; 223 untreated	Female = 105	Cogn assessment	164 SD=9	89 SD=7	Deficits in speed of cognition among hypertensive group.

Using Trail Making condition 2 and 3 of DFES (2001), Stroop Color-Word Test, and Verbal Fluency, Vasilopoulos and colleagues (2012) did not find a significant correlation between midlife hypertension and processing speed. In addition, their study did not report any significant difference in the speed of information processing between normotensives and hypertensives, treated or untreated hypertensives.

The deleterious impact of hypertension on the speed of information processing has been estimated through the calculation of the ES, which varies between small to large. For example, Waldstein and colleagues (1991) have found a medium ES (d=0. 51) of untreated HTN on tests of psychomotor abilities but a small ES (0.37) on the Digit Symbol Test. Calculating the ES using the standard deviation pooled when the sample size of the treatment (nt) and control (nc) are different (Lipdzey, 1990), one finds a small ES (0.38) of hypertension and speed of cognition from Saxby and colleagues' study (2003). There is a large ES (1.00) of borderline hypertension on the speed of information processing from Shehab and Abdulle's study (2011). However, Van den Berg and colleagues (2009) have also found a smaller effect size (0.2) of hypertension on the speed of information processing.

The slowing speed of information processing in individuals with hypertension is associated with the vulnerability of white matter and the presence of small cerebral diseases. The increased severity of periventricular white matter (Prins, et al., 2005, O'Brien, 2002) and hyperintense lesions in the gray matter of the thalamus and caudate (O'Brien, 2002) were mostly associated with declines in the speed of information processing in individuals with hypertension. For example, Thorvaldson and colleagues (2013) have found that white matter lesions in individuals with DBP was correlated with a decline in perceptual speed. In

addition, Gianaros and colleagues (2006) reported an association in men between increased SBP and short-term information processing and found that these individuals had smaller grey matter volume in the supplementary motor area and the adjacent superior frontal gyrus, the middle temporal gyrus, and the anterior cingulate. Jennings (2003) noted that regional cerebral blood flow (rCBF) changes in hypertensives have been related to a slow speed of information processing. These findings are consistent with the results of previous researchers, which have suggested that different white matter pathways play crucial roles in speed of information processing (Penke, et al., 2010 & Turken, et al., 2008).

3.3.2.6. HTN and Language

Language performance has been an important neurocognitive function assessed in individuals with hypertension. Some studies have examined verbal functions (e.g., comprehension, naming, reading, writing, speech) using some subtests of WAIS and other tests (e.g., BNT) (See Table 10).

Table 10: Studies Assessing the Relationship between HTN and Language.

Authors and years	N	Mean/SD age	Measure Used	Mean/SD SBP	Mean/SD DBP	Findings
Vasilopoulos, et al., 2012	1237	55.4 years	WASI Vocabulary			No significance difference between difference BP groups (Non, med, unMeds) and verbal abilities.
Knecht, et., 2009	377	64 SD=6.62	Boston Naming Test (BNT)-short Form	144 SD=18.79	84 SD=10.76	Linear relation between SBP and verbal abilities.
Elias, et al, 2004	529	46	Comprehension, Similarities, Vocabulary, Information, Arithmetics of WAIS			No significant relation of HTN and with crystalized/verbal abilities.
Waldstein, et al., 2005	733	70.6 SD=8.5	Boston Naming Test (BNT)	138.7 SD=20	82 SD=10.9	Both High SBP and DBP were associated with poorer confrontation naming in untreated hypertensive individuals.
Elias, et al, 1998	140	51 SD=7.63	Crystalized verbal: Comprehension, Similarities, Vocabulary, and Information of WAIS	118.8 SD=12.43	69.9 SD=7.72	No significant difference between hypertensive and normotensive in crystalized-Verbal mean slope.

Thorvaldsson, et al., 2011	382	70 years and over	Synonyms		Invert U shaped association between low BP High Blood pressure and verbal ability.

A few studies have found a significant correlation between hypertension and verbal functions such as verbal comprehension, speech, and writing (Vanderploeg et al., 1987). Using the WASI Vocabulary test, Vasilopoulos and colleagues (2012) did not find any significant correlation between midlife hypertension and verbal ability. Waldstein and colleagues (1991) have found a small ES (d=0.10) of HTN on measures of verbal skills. In addition, their study did not report any significant difference between normotensives and treated or untreated hypertensives.

Some studies have reported poor performance in verbal fluency in older individuals with hypertension (Kuusisto et al., 1993; Elias, et al., 1995). Assessing individuals with hypertension with the Synonyms Test, Thorvaldson and colleagues (2013) reported on the nonlinear effects of DBP on verbal function. In addition, Waldstein (2005) and his colleagues have noted a nonlinear association between DBP and naming ability as measured by BNT as well as a linear relation of DBP to expressive language as measured by Verbal Fluency Test.

These conflicting results on the relation of hypertension and verbal abilities have been identified with the insignificant effect size of hypertension on language (Vasilopoulos, et al., 2012). For example, Waldstein and colleagues (1991) have found a small ES (d=0.10) of HTN on measures of verbal skills. In this sense, a few neuroimaging studies have examined the association of hypertension with different brain areas involved in different verbal abilities. For example, Jennings (2003) has suggested that an increase in the left lateral prefrontal (Broca's area) regional cerebral blood flow (rCBF) is a predictor of poor performance in some verbal abilities. in addition, these conflicting findings can be attributed to the age of participants, with older participants performing more poorly than younger

participants (see Table 10). Finally, researchers have shown that crystalized or verbal abilities are "spared" compared to fluid abilities (Elias, et al., 2004).

3.3.2.7. HTN and Visual Spatial Abilities

Researchers have reported inconsistent findings on the relation between hypertension and different visuospatial abilities, for example, constructional abilities, spatial orientation, and drawing (See Table 11).

Table 11: Studies Assessing the Relationship Between HTN and Visual Spatial Abilities.

Authors	N	Mean/SD age	Measure Used	Mean/SD SBP	Mean/SD DBP	Findings
Shehab & Abdulle, 2011	Total=69 Normal=20 HTN=30 WCH=19	38.2SD=10.8	Spatial Span Test (SSPT) of Cambridge Neuropsychological Test Automated Battery (CANTAB).	155 SD =16		No difference between normotensive, White Coat HTN, and borderline HTN in mean value of SSPT.
Vasilopoulos, et al., 2012	1237	55.4 years	Hidden Figures Test Card Rotation Task			No difference between BP groups (No, meds, unmeds) and visual-spatial ability.
Knecht, et., 2009	377	64 SD=6.62	RCFT	144 SD=18.79	84 SD=10.76	Association between SBP and spatial skills.
Waldstein, et al., 2005	733	70.6 SD=8.5	BVRT	138.7 SD=20	82 SD=10.9	Both high SBP and DBP associated with poorer performance in perceptuo-motor speed test.
Elias, et al, 1998	140	51 SD=7.63	Visualization-Performance of WAIS: Picture Completion, Picture Arrangement, Block Design, and Object Assembly.	118.8 SD=12.43	69.9 SD=7.72	Significant difference between hypertension and normotensive in mean slope of visualization-Performance.

Thorvaldsson, et al., 2011	382	70 yrs and over	Figure Identification	Invert U shaped association between low BP High Blood pressure and measure of visual spatial ability.
Brady, et al., 2005	357	67	Speeded pattern comparison Test of neurobehavioral Evaluation System Figure copy Test of CERAD	Significant difference between controlled and uncontrolled HTN in measure of visual spatial ability.

However, many studies have suggested that hypertension leads to poor performance in some visual spatial skills (Thorvaldsson, et al., 2012; Brady, et al., 2005; Elias, et al., 1998; Waldstein 1991). These inconsistent results have also been shown through the variation in the effect size of hypertension on visuospatial abilities. For example, Waldstein and colleagues (1991) have noted a medium ES (d=0.47) of untreated HTN on measures of visuoperceptual abilities. However, the ES was large in a sample of untreated HTN on constructional abilities (d=0.79) but was small (d=0.31) on Block Design. Calculating the ES using the standard deviation pooled when the sample size of the treatment (nt) and control (nc) are the same (Lipdzey, 1990), one finds a small effect size (0.18) of hypertension on visual spatial skills inBrady and colleagues' study (2005). Some studies have found that lower posterior parietal regional cerebral blood flow (rCBF) was associated with a decline in some visual spatial abilities (Jennings, 2003). Finally, Haley and colleagues (2008) have noted that hypertensives with a decreased size either of the right inferior parietal lobule, the right inferior temporal gyrus, or the posterior cingulate had poor performance in visuospatial attention and memory tasks.

3.3.3. Summary of the Relationship between Hypertension and Cognitive Function

A majority of studies have found poorer performance in hypertensives than normotensives in some cognitive functions. In terms of effect size, deficit in cognitive function has been greatest in executive functions, memory, speed of information processing, attention, and visual spatial skills. Conversely, measures of language did not have a significant relationship to high blood pressure. The relationship between hypertension and dementia or cognitive function has been presented as an association or correlation rather than

as causal. Many articles have reported various types of significant correlations between hypertension and various cognitive functions (See Table 6 to Table 11). Studies have suggested different directions and forms of the relationship between hypertension and cognitive function. A wide range of studies has found negative or inverse correlations between hypertension and cognitive decline (i.e., when BP increases, cognitive function decreases) (Pandav, et al., 2003). However, other researchers have found positive correlations (i. e, when BP changes, cognitive function changes in the same direction) between hypertension and cognitive function (Guo, et al, 1997; Cacciatore, et al., 1997). Experts have also noted that the curve of cognitive decline in individuals with hypertension over the lifespan was a "J-shaped" or "U-shaped" correlation (Thorvaldsson, et al., 2012; Molander, et al, 2010; Novak & Hajjar, 2010; Waldstein, et al., 2005; Bohannon, et al., 2002; Knopman, et al., 2001; Glynn, et al., 1999). Waldstein (2005; 1995) has suggested that young and old individuals with hypertension are more likely to perform more poorly in neuropsychological measures than middle age individuals with hypertension. Finally, many studies have found that these associations between hypertension and cognitive function were non-linear correlations (i.e., an association where all the points on the scatter diagram tend to form a smooth curve) (Novak & Hajjar, 2012, 2010; Thorvaldsson, et al., 2012; Waldstein, et al., 2005). The effect of hypertension on different cognitive functions, the impact of age, and the duration of hypertension were tested in this dissertation.

3.4. Treatment of Hypertension

Hypertension is known for its insidious progression, its effects on various major organs, and its association with cerebrovascular risks, dementia, and vascular cognitive

impairment. In terms of its treatment, the Seventh Report of the Joint National Committee (JNC7, 2003) has recommended that the treatments of individuals with hypertension include the following elements: routine laboratory tests, lifestyle modification, and pharmacologic treatment. Concerning laboratory tests, experts from this same national committee have suggested that the clinician request the following laboratory diagnostic tests in hypertensives before starting any type of therapy: electrocardiogram, blood glucose, hematocrit, and urinalysis, as well as creatinine (e.g., GFR), serum potassium, calcium, lipids, high and low density lipoprotein cholesterol and triglycerides (JNC 7, 2003). The Guide to Management of Hypertension (2010) has suggested the following physical examinations of the cardiovascular and endocrine systems: pulse rate, rhythm, character, jugular venous pulse and pressure, evidence of wheezing as well as edema, evidence of arterial disease, abnormality of optic fundi, focal neurological signs, waist circumference, BMI, and thyroid function. All these physical and laboratory tests have been found to be important in the diagnosis, treatment, and management of hypertension.

Life style modifications have been proposed by experts of evidence-based medicine as a "critical" means to prevent and manage hypertension. For example, the Seventh Report of the Joint National Committee (JNC7, 2003) and other researchers (Kaplan and Victor, 2010) have suggested the adoption of the following major lifestyle modifications: (1) Dietary Approaches to Stop Hypertension (DASH), such as a diet high in nitrate and fiber, low in fat or free of it, a lipid-lowering diet, balanced protein intake, and a diet rich in fruits and vegetables; (2) weight reduction (i.e., BMI between 18.5 and 24.5 Kg/m2); (3) avoidance of smoking; (4) dietary sodium reduction (less than 100 mmol); (5) alcohol and caffeine

consumption moderation (less than 2 drinks for men or 1 drink for women); (6) physical activity (i.e., at least 30 minutes every day); (7) supplementation of potassium, calcium, and magnesium. Combinations of lifestyle modifications and pharmacological treatments have been found to reduce blood pressure.

Pharmacologic treatments of hypertension include drugs such as diuretics, angiotensin- converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), renin inhibitors, calcium-channel blockers (CCBs), alpha and beta adrenoceptor-blocking agents (BB), centrally acting adrenergic drugs, and vasodilators (Harvey, Clark, et al., 2012; Kaplan & Victor, 2010; JNC7, 2003). In terms of the algorithm for the treatment of hypertension, the JNC7 (2003) has suggested the following initial drugs when there are no other comorbidity conditions: (1) lifestyle modifications for pre-hypertensive patients (i.e., BP less than 140/90 mmHg or <130/80 mmHg with diabetes or chronic kidney disease); (2) Thiazide diuretics or possibly ACEI, ARB, BB, CCB or combination for stage 1 hypertension; (3) two-drug combination (thiazide diuretics and ACEI, or ARB, or BB, or CCB) for stage 2 hypertension.

Many treatment guidelines recommend that drug options for the control of blood pressure consider whether the patient has hypertension with or without any other medical conditions. For example, Hypertension Diagnosis and Treatment Guidelines (2012) has recommended the following pharmacologic options for hypertensive patients who do not have a cardiovascular disease: (1) first line therapy includes a combination of ACEI and a diuretic or ACEI; (2) second line is the increase in the dose of ACEI; (3) third line is the addition of CCB; (4) fourth line is the addition of ARB or BB; (5) fifth is the addition of an

Aldosterone antagonist or alpha2-adrenergic agonist or vasodilator. In treating hypertensives with a history of other medical conditions, JNC (2003) has recommended the following antihypertensives: (1) diuretics, BB, ACEI, ARB, and Aldosterone for HTN with heart failure; (2) BB and ACEI for HTN with postmyocardial infarction; (3) diuretics, BB, ACEI, and CCB for HTN with high coronary disease risk; (4) diuretics, BB, ACEI, ARB, and CCB for HTN with diabetes; (5) ACEI and ARB for HTN with chronic kidney disease; (6) diuretics and ACEI for HTN with stroke. Finally, pharmacologic treatment depends on the type of hypertension, the age, the gender, and the race of the patient as well as on cardiovascular disease risks and the previous medical history and condition.

Related to the efficacy of antihypertensives, some researchers have indicated that the primary goal of these medications is to decrease blood pressure in order to prevent dangerous cardiovascular risks (Kaplan & Victor, 2010). In addition, there is conflicting evidence about the progressive reduction of dementia and cognitive deficits by using effective antihypertensive therapy. Animal and human studies have reported that some antihypertensive drugs were beneficial in lowering the incidence of dementia and in protecting against cognitive decline (Yasar et al., 2008; Zhang, et al., 2007; Skoog, et al., 2005). However, some researchers did not report any "neuroprotective effect" of antihypertensives on dementia and cognitive function because they were taken "too little, too late" (Kaplan & Victor, 2010).

The conflicting relation between antihypertensive medication and dementia and cognitive decline can be approached by understanding three important facets of this association: awareness, treatment, and control. The awareness of hypertension has been

defined as the knowledge of having hypertension after being diagnosed by a physician or health professional. The treatment of hypertension is understood as the taking of antihypertensives or using lifestyle modification or using both therapies as way to reduce one's blood pressure. Finally, the control of hypertension has been understood as resulting from the treatment of hypertension (i.e., reducing the systolic blood pressure to less than 140 mm Hg and the diastolic blood pressure to less than 90 mm Hg) (Sug Yoon, 2012; Kaplan & Victor, 2010). For example, the U.S Department of Health and Human Services (2012) reported that in 2009-2010, 81.9% of adults with hypertension were aware of their hypertensive status, 76.4% were taking antihypertensive medications, while only 53% had controlled hypertension.

The National Center for Health Statistics of 2012 (NCHS) from the Center for Disease Control Prevention has noted disparities of age, sex, and race in regard to the awareness, treatment, and control of hypertension in 2009-2010. Concerning the awareness of hypertension, the NCHS (2012) have reported that individuals between 18 and 39 of age (58.7%), men (79.6%), and Hispanic (77.7%) have lower awareness of their hypertension than those from 40 years old and over (84.1%), women (84.9%), whites (81.4) and blacks (87.0%). In terms of the treatment of hypertension, those between 18 and 39 of age (46%), men (73.1%), and hispanic (69.6%) were found to be less likely to take medications than those in the 40-59 group (77.1%), those 60 and over (80.7%), women (80.6%), whites (76.6%), and blacks (79.7%). Finally, related to the control of hypertension, those between the age of 18-39 (32.8%), men (50.4%), and Hispanics (40.7%) were less likely to have

controlled their hypertension than individuals with hypertension aged 40-59 (55.7%), 60 and over (54.9%), women (57.5%), blacks (47.9%), and whites (56.3%).

These data suggest that adults with hypertension between 18 and 39 of age, who are men, and hispanic are more likely to be unaware of and to have untreated and uncontrolled hypertension compared to those aged 40 and over, women, and whites. In addition, blacks were less likely to control their hypertension than whites (Sug Yoon, et al, 2012). These findings point out possible contributions of endogenous factors (i.e., factors inside the model) and exogenous factors (i.e., factors outside the model) in the awareness, treatment, and control of hypertension. Finally, it may be suggested that hypertension continues to have a deleterious impact regardless of whether the person is being aware or unaware, treated or untreated, controlled or uncontrolled. However, studies have shown that the severity of the impact of hypertension was different among those unaware, untreated, and uncontrolled.

Poorer performance in neurocognitive measures and dementia have been reported mostly in individuals who were either unaware of their hypertension or had unmedicated and uncontrolled hypertension. For example, Waldstein and colleagues (1991) found a large effect size (d=0.96) on memory, comparing normotensive individuals to unaware and untreated individuals with hypertension. Therefore, the diagnosis of hypertension has been considered as the first step to the treatment of hypertension, and taking antihypertensive drugs was also found to enhance the control of hypertension (Khan, et al., 2005). In addition, a wide range of studies have observed that untreated individuals with hypertension had a higher incidence of dementia and cognitive decline (Baskys & Cheng, 2012; Novak & Hajjar, 2010; Birns & Kalra, 2009). Finally, other studies have found that poorly controlled

hypertension was a predictive factor of dementia and cognitive decline in some elderly individuals (Cherubini, et al., 2010). However, as Thorvaldsson and colleagues (2012) have noted, the correlation between untreated and uncontrolled hypertension with dementia and cognitive deficits remained "less clear."

Experts have related these conflicting results to different confounding variables. Some researchers have noted that the type of anti-hypertensive medications used, their mechanisms of action, and their pharmacokinetic characteristics may contribute to these confounding effects (Novak & Hajjar, 2010; Anson & Para, 2005). Clark and colleagues (2012) have indicated the following mechanism of actions for some major antihypertensives. For example, diuretics reduce blood pressure by increasing sodium and water excretion, which leads to a decrease in blood volume and cardiac output. Beta-blockers reduce blood pressure by reducing cardiac output, sympathetic outflow from the central nervous system, and by inhibiting the release of renin from the kidney. This reduction of renin leads to a decrease of the formation of angiotensin II and the secretion of aldosterone. The ACE inhibitors lower blood pressure by inhibiting the conversion of angiotensin I to angiotensin II, by decreasing vasoconstriction, and by breaking down the bradykinin (i.e., production of nitric oxide and prostacyclin by blood vessels). Like the ACEIs, the angiotension-receptor blockers (ARBs) block the AT1 receptors by using angiotensin II. Finally, the calcium channel blockers are involved in promoting the smoothness of muscle and in the contraction of the heart muscle.

Beside these different mechanisms of action of antihypertensive medications, the sample studied, the cognitive function assessed, and the design used in the study have been

found to explain the conflicting findings (Novak & Hajjar, 2010). For example, study design (e.g., observational method and randomized trails) has been shown to be important in understanding the association between hypertension and the risk of dementia/cognitive decline (Novak & Hajjar, 2010; Duron & Hanon, 2010). Many meta-analyses have reported that observational studies (e.g., The Rotterdam Study and the Honolulu Asia Aging study) have found a protective effect of antihypertensives on preventing vascular dementia and cognitive function (Novak & Hajjar, 2010; Birns & Kalra, 2009; Duron & Hanon, 2008). On the other hand, different review articles have reported inconsistent findings with non-randomized trials (Novak & Hajjar, 2010; Duron & Hanon, 2008).

After reviewing major studies of randomized trails, Duron and Hanon (2008) reported that Systolic Hypertension in the Europe Trail Study (SYST-EUR 2, Forette, et al., 1998) found that two years of treatment with the antihypertensives (calcium blockers, CEIs, and beta-blockers) significantly reduced the incidence of dementia 50% in 60 year-old patients with isolated systolic blood pressure. The same study (SYST-EUR 2, 1998) noted a significant reduction of dementia (55%) in patients who were treated with CCBs, ACEIs, diuretics, and other antihypertensives for four years. In addition, Perindopril Protection against Recurrent Stroke Study (Tzourio, 2003) also reported significant reduction of cognitive decline (19%), dementia (23%), and vascular dementia related to stroke (34%) in patients treated with the combination of ACEIs and diuretics for four years. Finally, another major study, the Heart Outcome Prevention Evaluation (Bosch, et al., 2002), found that the treatment of hypertension with ACEIs for 4.5 years reduced cognitive decline associated with stroke by 41%.

Some findings of these studies can be interpreted only by taking into consideration the difference between statistical significance and clinical significance. Statistical significance is to be understood in the context of hypothesis testing, expressing the probability that the results of a study (i.e., 0.05 or 0.01) are due to chance. However, clinical significance is the extent to which the effect of a treatment makes an important difference to the patients or has practical value in helping the patient become functional (Kadzin, 2003). In this sense, the results of some trials appear to have good statistical significance but do not have clinical significance. For example, the findings of Perindopril Protection against Recurrent Stroke Study (Tzourio, 2003) have good statistical significance because there is a strong probability that they are not due to chance. The treatment significantly reduced cognitive decline, dementia, and vascular dementia related to stroke. However, this statistical significance does not appear to be clinically significant because the percentage reduction of different dysfunctions is not large enough for the drug to be selected for future treatment compared to other drugs.

Other meta-analyses have reported that some non-randomized studies did not find any significant association between the treatment with antihypertensives and the reduction of blood pressure in decreasing the risk of developing dementia and of cognitive decline (Bierkenharg et al., 2006). For example, some major studies of antihypertensives did not report any significant protective effect of these medications on dementia and cognitive decline. The Hypertension in the Very Elderly Trial cognitive function assessment study (Peters, et al., 2008) did not find any significant difference in cognitive function between hypertensives who were treated either with ACEI (peridopril) or with a placebo for 2.2 years.

The Systolic Hypertension in the Elderly Program study (Applegate, et al., 1996) found that taking diuretics and beta-blockers for 14 years did not prevent old patients (i.e., over 80 of age) with isolated systolic blood pressure suffering from stroke and vascular dementia. In addition, the Medical Research Council's study (Prince, et al., 1996) has reported that individuals with hypertension and who were treated with beta-blockers or diuretics for 5.8 years were not protected from cognitive decline. The Study of Cognition and Prognosis in the Elderly (SCOPE, 2003) did not find a significant difference in the effect of the placebos and diuretics used for 3.7 years in the reduction of dementia (only a 7% reduction). Finally, the Prevention Regimen for Effectively Avoiding Second Stroke study (Diener, et al., 2008) found that reduction of blood pressure during 2.4 years with ARB did not significantly protect hypertensives from cognitive decline.

3.5. Variables Influencing the Relationship Between Hypertension and Cognitive Function

Researchers have identified various factors that affect the direction and strength of the association between hypertension and cognitive function and dementia. Studies have found that age, education, comorbidities with cerebrovascular diseases (CVD), metabolic diseases, and psychiatric diseases affect cognitive function in hypertensives (Vasilopoulos, 2012; Waldstein, 2003). For example, Waldstein (2003) has reported a variation of results between young to middle-aged hypertensives (20-60 years) and older hypertensives (60 and older). On the one hand, these varying findings have been explained by structural and hormonal changes in the normal aging brain. For example, neuroimaging investigations have identified the following changes in the aging human brain: (1) 10% loss of neurons in the neocortex over life time (Schmitz & Hof, 2007); (2) shrinkage of brain volume mostly in the frontal and

the temporal lobes (e.g., hippocampus) entorhinal cortices, the thalamus, the putamen, the nucleus accumbens, and the enlargement of the ventricular system (Fjell & Walhovd, 2010); (3) a decrease in grey matter density, a reduction of the length of myelinated axons of white matter, and a lower number of synapses (Fjell & Walhovd, 2010); (4) the presence of arteriosclerosis and neurofibrillary tangles; (5) neurotransmitter changes (e.g., decreased dopamine, serotonin, and glutamate). All these neuroanatomical and hormonal changes have been associated with significant cognitive deficits in healthy aging brain. On the other hand, Waldstein (2003) did not attribute poor cognitive performance in older individuals with hypertension only to physiological changes but also to early onset of hypertension, which sometimes remains undiscovered and untreated.

Education has been found to affect the association between hypertension and cognitive function. For example, Israeli-Korn and colleagues (2009), who examined the correlation between age, sex, and education and vascular risks and Alzheimer's disease in a sample of individuals over 65 years old in Israel, found that hypertension, a low level of education, and being female were associated with dementia. In addition, other studies have reported the protective effect of education in cognitive decline in individuals with hypertension (Inaba, et al., 2011; McCaffery, et al., 2008; Knetcht, et al., 2007; Vicario, et al., 2005; Insel, et al., 2005; Waldstein, 2003). However, other studies did not find any significant association either between education and cognitive decline or between education and prevalence of hypertension (Vasilopoulos, et al., 2012; Kilander, et al., 1998). For example, the Framigham Offspring Study (Loucks, et al., 2011) found an inverse correlation

between education and systolic blood pressure in individuals with 30 years of high blood pressure.

Comorbidity of hypertension either with metabolic syndrome, substance abuse, or with some psychiatric disease has been found to exacerbate a deficit in cognitive function. In terms of metabolic syndrome, Mosby's Medical Dictionary (2013) and the World Health Organization (1999) have defined this syndrome as the combination of at least three of the following: increase of waist circumference (i.e., > 40 inches for men and > 35 inches for women); elevated triglycerides (i.e., >150 mg/dL); elevated blood pressure (i.e., 130/85 mm Hg); increase of fasting glucose (i.e., >100mg/dL); reduced HDL cholesterol (i.e., <40mg/dL for men and <50 mg/dL for women). Many studies have reported that hypertension and metabolic disturbances were strong risk factors for cognitive deficits and diseases (Kuo, et al., 2005; Vicario, et al, 2005; Waldstein, 2003; Kilander, et al., 1998). For example, Kuo and colleagues (2005) have reported faster cognitive decline in individuals with both hypertension and diabetes mellitus. In addition, researchers have noted marked cognitive deficit in individuals with hypertension, cerebrovascular diseases, and depression. Insel and colleagues (2005) have found significant cognitive deficit in individuals with hypertension in comorbidity with diabetes mellitus, stroke, and depression.

Physical activities (i.e., aerobic exercise) and leisure activities have been found either to reduce hypertension or to improve cognitive function. On the one hand, studies have reported cognitive improvement in individuals with hypertension who regularly exercised (Gregory, Parker, & Thompson, 2012). For example, Smith and colleagues found significant neurocognitive improvement in elderly individuals with high systolic blood pressure who

controlled their diet and exercised (Smith, et al., 2010). In addition, Fiocco and colleagues (2011) reported that low sodium intake and physical activity in hypertensives were associated with cognitive maintenance. On the other hand, numerous studies have reported the benefit of physical activity (e.g., walking, running, marathon, treadmill running, swimming, football, and cardiorespiratory fitness) and leisure activities in controlling hypertension (Cunha & Jardim, 2012; Dimeo, et al, 2012; Fagar, 2012; Parati & Ochoa, 2012; Nualnim, et al., 2012; Thannassouli, et al, 2012; Shook, et al., 2012; Lima, et al., 2011; Rosi, et al., 2011; Lee, et al., 2010). Finally, researchers have noted that yoga therapy reduced blood pressure and other risk factors of blood pressure (e.g., blood glucose level, cholesterol, and body weight) (Okonta, 2012; Cohen, Raymond, Townsend, 2007).

Researchers have presented possible mechanisms through which physical activities and exercise are beneficial in controlling hypertension. Rossi and colleagues (2012) have shown that physical activity and exercise have a significant impact on the risk factors of hypertension. This review found that exercise increased glucose tolerance, decreased BMI, lowered platelet activity, and diabetes mellitus type 2. In addition, exercise was found to change total peripheral resistance and to reduce plasma volume and the cardiac index. In addition, studies have noted that physical activity and exercise had a significant benefit on the important pathways involved in the pathogenesis of hypertension. For example, Fagard (2006) reported that exercise reduced vascular resistance, which is directed by the sympathetic nervous system and the renin-angiotensin systems. Physical activity has been involved in enhancing endothelial function (e.g., improving antegrade vascular shear stress or force of friction of blood in the artery) and arterial stiffness (Rossi, et al., 2012). Finally,

Hansen and colleagues (2011) have reported that exercise training improved positively the balance between vasodilation and vasoconstriction in individuals with hypertension. Beside these variables which improve cognitive function in individuals with hypertension, there are other factors which have been found to control hypertension.

3.6. Other Variables Found to Control Hypertension

Substantial evidence exists that supports a link between some variables (e.g., health literacy, occupation, and spirituality) and the control of hypertension. Health literacy, defined by the American Medical Association (2004) as the ability for a person to obtain, process, and to understand basic health information and activities in order to respond adequately to issues related to one's health, has been shown to be beneficial in controlling hypertension. Using the Functional Health Literacy (FHL), Critical Health Literacy (CHL), and Hypertension Knowledge (HK), Shibuya and colleagues (2011) found that a lower health literacy and knowledge of hypertension was correlated with poor health status and blood pressure in a sample of middle-aged Japanese with hypertension. Other studies have indicated that health literacy in association with education and motivation were important predictors in controlling hypertension (Pandit, et al., 2009; Levinthal, et al., 2007). Neafsey and colleagues (2008) have noted that health literacy was an important factor in older adults in the awareness, pharmacologic treatment, lifestyle modifications, and in the control of hypertension.

Occupation has also been reported to be a preventive factor in the management and control of hypertension. Davila and colleagues (2012) have found a high prevalence and a low control of hypertension in individuals with a higher stress job (e.g., protective service

occupations). Some studies found that some occupations among seniors (e.g., professionals, salespeople, private household cleaning service workers, personal workers, mechanics, construction trades, and precision production workers) were significantly associated with hypertension (Leigh & Du, 2009). Some researchers have suggested high level of stress, psychological demands, and low decision latitude to be predictors of the increase of blood pressure in high job strain workers (Davila, et al., 2012). Contrary to these findings, other studies did not report any association between high job-strain and the genesis of hypertension (Kivimaki, et al., 2007; Ducher, Cerutti, Chatellier, & Fauvel, 2006). In terms of the control of hypertension, Davila and colleagues (2012) found that executive, administrative, and managerial workers had higher control of hypertension compared with protective service workers. In this sense, occupation appears to matter in the awareness, treatment, and control of hypertension.

Attendance at religious and spiritual activities (e.g., prayer, meditation, and yoga) have been proposed to be active in reducing high blood pressure. Findings related to these correlations have been conflicting with some studies reporting stronger correlations while others did not find any significant correlation. For example, numerous studies have indicated that religious attendance was a strong predictor of reduction of high blood pressure (Bell, et al., 2012; Chung, et al., 2012; Naewbood, et al., 2010; Sorensen, et al., 2011; Baig, Mangione, Sorrell-Thomsposon, & Miranda, 2010; Lewis, et al., 2008, Giaquinto & Spiridigliozzi, 2007; Gillum, et al., 2006; Tartaro, et al., 2005, Hill, et al., 2004; Brown, 2000). Buck and colleagues (2009) reported that forgiveness and the meaning of religion in other life's activities were both negatively related to DBP and hypertension while meaning of

religion in other life's activities and forgiveness of self were found to positively correlate with blood pressure and the reduction of hypertension. Buck and colleagues (2010) did not report any significant association between religious attendance and hypertension in a sample of young individuals (i.e., an average age of 43 years) using the following measures--Spiritual Attendance Beliefs, Social Attendance Beliefs, Positive and Negative Religious Coping, Religious Saliency, The Congregational Support, and Forgiveness of Others and Self Measures of Religiosity--. Fitchett and colleagues (2009) also found that daily spiritual experiences were not associated with SBP or hypertension in midlife women. Some experts have attributed these conflicting findings to differences in the age of the participants in different studies with those including older hypertensives reporting a more significant correlation than those with younger participants (Buck, Williams, Musick, & Sternthal, 2009).

In summary, different types of hypertension, its pathophysiology, and its deleterious impact on major organs (e.g., brain, heart, and kidney) were reviewed. Numerous researchers have supported the relationship between hypertension and dementia/cognitive decline. Substantial evidence exists that engaging in different lifestyle modifications and using pharmacologic treatments that controlled hypertension had protective effects on neurocognitive deficits. These findings, however, are still conflicting and do not present a clear-cut answer to the question. In this sense, researchers have found different predictors which affect the strength and the direction of the relation of hypertension and cognitive function. It could be concluded that hypertension has insidious and deleterious effects on "vascular reserve capacity" (i.e., pressure autoregulation and C02 vasoreactivity) and

cognitive function (Novak & Hajjar, 2010). Therefore, enhanced understanding of the construct of reserve and its impact in protecting individuals from consequences of neuropathology and cognitive decline can contribute in the development of new treatment strategies for cognitive impairment in individuals with hypertension.

3.7. Significance of the Study

The present study incorporates cerebrovascular and cognitive frameworks to examine the influence of cognitive reserve (namely early environment, educational and occupational attainment levels, the IQ, and the participation in physical and leisure activities) on the relationship between individuals with clinical hypertension and their cognitive functions (See conceptual model, Figure 2). In attempt to examine this protective role played by cognitive reserve between hypertension and deficits in cognitive functions, this study had two primary objectives: (a) to compare cognitive functions in individuals with clinical hypertension (i.e., those either aware or unaware, untreated or treated, and controlled or uncontrolled) with those without hypertension; and (b) to determine whether any such differences in cognitive functions could be attributable to differences in cognitive reserve.

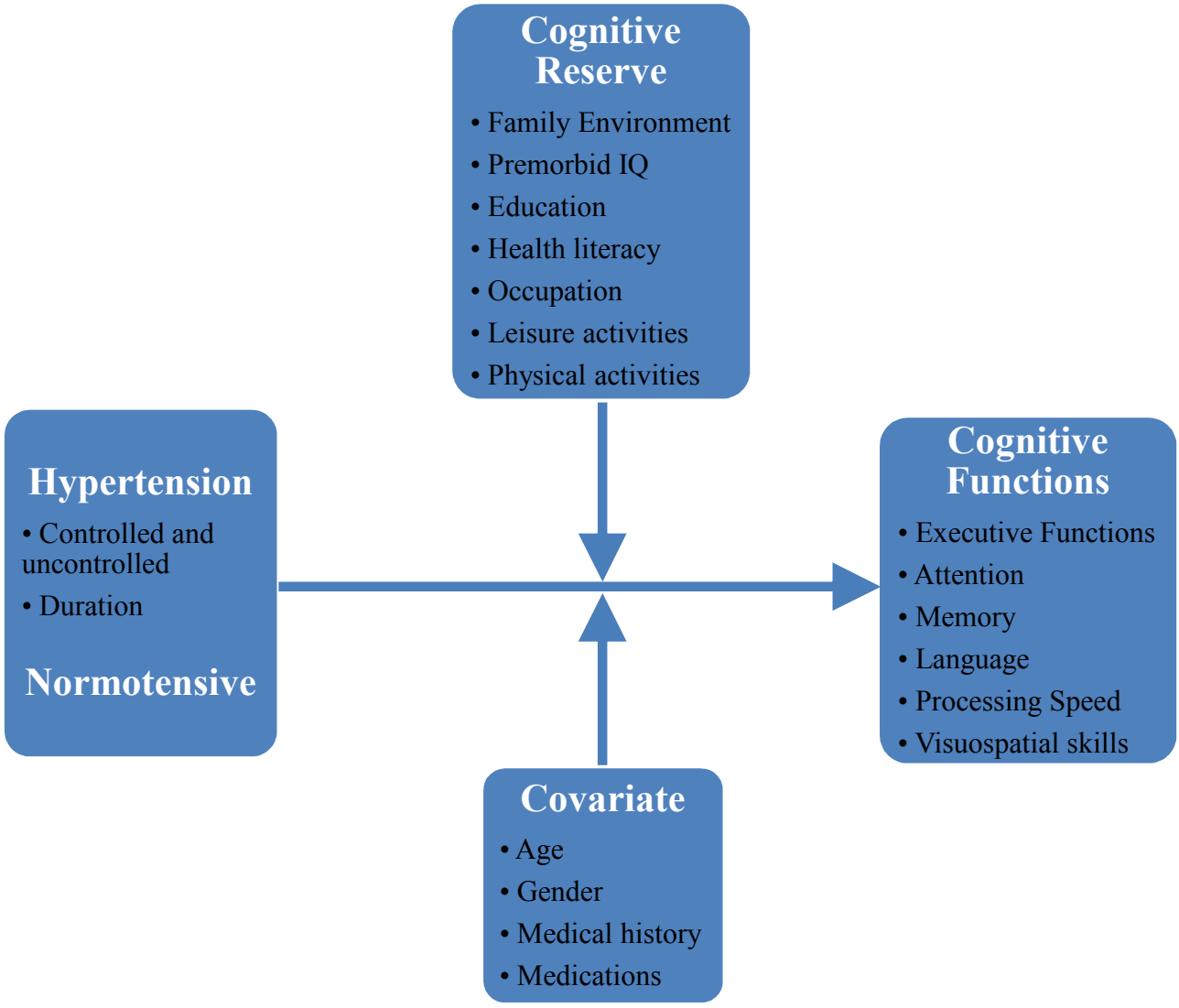


Figure 2: Conceptual Model of the Study

There are both practical and theoretical reasons for conducting this study. From a practical perspective, knowing the protective role of cognitive reserve will provide valuable information in the remediation and prevention of cognitive decline in individuals with clinical hypertension. This study may be useful for any hypertensive person of any developmental stage who participates in cognitively challenging activities because previous

evidence suggests that these activities maintain the reserve, reduce age-related cognitive decline, and protect against the risk of developing dementia or vascular dementia. This study may provide some evidence to individuals with clinical hypertension of the importance of engaging in healthy cognitive habits such as being exposed to enriched environments, participating in aerobic exercise and leisure activities, and having intellectually stimulating occupations. Contrary to the popular saying "you cannot teach an old dog new tricks", this study will show that older individuals with hypertension can learn new challenging cognitive activities which can maintain their cognitive functions. This research, in sum, may support the practice of remediation and compensation strategies to improve cognitive deficits in individuals with clinical hypertension.

On a theoretical level, this study integrated a number of cognitive activities, -- IQ, education, occupation, physical and leisure activities, -- which are factors that contribute to cognitive reserve and decrease the risk for dementia or cognitive decline. Moreover, we may better understand whether higher levels of education, participation in physical and leisure activities, and high occupational attainment and IQ lead to enhanced cognitive reserve and to protection against vascular cognitive impairment in individuals with hypertension. This study may in turn provide information on whether these proxies of cognitive reserve are more strongly related to cognitive function than pharmacological treatments of hypertension. This study may contribute to the literature on the association between cognitive reserve and cognitive deficits in clinical hypertension. Although there is little empirical evidence to date about cognitive reserve in individuals with clinical hypertension, improvements in certain areas have been consistently related to the successful management of clinical hypertension.

These includes areas of physical activities (Gregory, Parker, & Thomspson, 2012; Smith, et al., 2010) and leisure activities (Cunha & Jardim, 2012; Dimeo, et al., 2012), and a high level of education (Inaba, et al., 2011; Israel-Korn, et al., 2009; Vicario, et al., 2005; Waldstein, 2003), health literacy (Shibuya, et al., 2011), and high attendance at religious and spiritual activities (Bell, et al., 2012, Chung, et al., 2012). Considerable evidence exists to support the hypothesis that high cognitive reserve can serve to maintain cognitive function in individuals with clinical hypertension. Numerous studies have shown that cognitive reserve may contribute to the delay of the expression of dementia and cognitive decline (Stern, 2012, 2009, 2006; Tucker-Drob, et al., 2009; Ngandu et al., 2007; Scarmeas, et al., 2006; Wilson, et al., 2003). The results of the current study may contribute to our understanding of this complex association.

The hypotheses to be tested in this study were the following:

Hypothesis 1: Measures of cognitive functions will be highly intercorrelated.

Hypothesis 2: Hypertensive participants will demonstrate lower cognitive function than normotensive participants.

Hypothesis 3: Hypertensive participants will demonstrate lower cognitive function than normotensive participants even while controlling for age, gender, medications, and medical conditions, and metabolic syndrome.

Hypothesis 4: Measures of cognitive reserve (i.e., early environment, IQ, education, occupation, leisure and physical activity) will be highly intercorrelated.

Hypothesis 5: Cognitive functions will be correlated with indicators of cognitive reserve.

Hypothesis 6: Cognitive reserve indicators will moderate the impact of hypertension on cognitive functions.

Hypothesis 7: Cognitive function will be better for those hypertensive individuals (1) who have controlled hypertension than those who have uncontrolled hypertension; and (2) for those with a shorter duration of hypertension (i.e., 10 years or less) than those with a longer duration of hypertension (More than 10 years).

CHAPTER 4: METHODS

4.1. Participants

One hundred and fifty (150) participants of average age 72.53 years (SD= 13.71 years) were recruited via phone calls and letters sent to pastors of different parishes and religious superiors of various religious retirement houses (i.e., priests and nuns) and other nursing homes in Michigan and Illinois. Religious superiors/directors of all these houses were required to consult with individual members of their charges to confirm their desire to participate. Participants were asked to give their name to the head nurse and a meeting was organized in each community to explain to the residents about the study.

All participants were required to satisfy the following inclusion criteria: (a) being over 45 years old; (b) being able to consent personally; (c) an adequate level of mental status as assessed by any score equal to or greater than 25 on Mini-Mental Status Exam (MMSE) administered by the investigator. Participant were excluded (a) if s/he was a prisoner and/or pregnant; (b) s/he had history of neurocognitive disorder (i.e., moderate or severe dementia), transitional states like mild cognitive impairment (MCI), stroke, alcoholism, drug abuse, and thought disorder (schizophrenia) as evidenced by medical records; (c) s/he had a medically complicated disease which makes the participant unable to consent as evidenced by the person's medical record.

4.2. Measures (See Appendix A)

4.2.1. Self-Report Behavioral Health Measures

Since depression, anxiety, and alcohol are well-known behavioral health disorders in geriatric population, we used the Patient Health Questionnaire to measure both depression and anxiety. These scores were used as covariates in this study.

Patient Health Questionnaire (PHQ): This measure is a self-report measure which assesses symptoms of depression and anxiety over the previous two weeks. Clinical and research evidence have reported the highest factorial validity for items with loading factors of 0.58 to 0.78 for all the nine depression items and 0.69 to 0.81 for all the seven anxiety items. PHQ is psychometrically known for its optimized sensitivity (89%) and specificity (82%) for Generalized Anxiety (Spitzer, et al., 2006). Depression and the anxiety severity is assessed on the following Likert scale: 0 as not at all; 1 as several days; 2 as more than half the days; and 3 as nearly every day. The measure of depression (PH9) has a range from 0-27 with a score of 5 describing mild depression, 10 as moderate, 15 as moderately severe, and 20 as severe depression. In addition, the measure of generalized anxiety disorder (GAD-7) has a range from 0-21 and score of 5, 10, and 15 representing cutoffs for mild, moderate, and severe anxiety respectively. In this study, a cutoff of 20 and 15 will was used as representing depression and anxiety respectively.

Symptom Checklist (SC): This measure evaluates neuropsychological symptoms based on current experience on a scale of 0 to 10, with zero being no current experience of the symptom and 10 being the worst experience of the symptoms (Hafkenscheid, 1993). The Symptom Checklist provides an overview of individual self-rating and intensity at a specific point of time for each cognitive function (e.g., executive function, attention, memory,

language, and processing speed of information). This measure compared the difference between self-rating and performance in a neuropsychological assessment.

4.2.2. Measurement of Blood Pressure

Blood pressure measure: Blood pressure was measured by an experienced clinician (e.g., registered nurse, physician) using a mercury or aneroid, hybrid, or electronic sphygmomanometer at the nursing home or residence. As recommended by the American Heart Association (AHA, 2005) and the Seventh Report of the Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure (JNC7, 2003), the individual were seated quietly for at least five minutes and the blood pressure was measured while the individual was either seated or standing with feet on the floor and the arm supported at one's heart level. The recommended cuff sizes for accurate measurement of blood pressure was at least 80 percent of the person's arm circumference. The AHA and the JNC7 propose at least two measurements of blood pressure to avoid various types of variations (e.g., short-term, daytime, diurnal, seasonal, and white-coat effect). In this study, three measurements of blood pressure taken three days or three Sundays consecutively were required to determine an individual's blood pressure.

Hypertension: In this study, clinical hypertension was defined as (1) the condition of unmedicated hypertensive individuals with mean systolic readings greater than or equal to 140 mm Hg and/or a diastolic readings greater than or equal to 90 mm Hg who were aware or unaware of their hypertension; (2) the condition of the medicated hypertensives with controlled or uncontrolled hypertension (i.e., individuals who reported any antihypertensive medication use, regardless of their current blood pressure readings; and (3) the condition of

normotensive participants with both normal blood pressure (i.e., BP below 120/80) and treated or untreated pre-hypertensives (i.e., BP between 120/80 and 139/89). In this study, blood pressure (SBP and DBP) was participants was considered hypertensive or having uncontrolled blood pressure only after three systolic readings greater than or equal to 140 mmHg and/or three diastolic readings greater than or equal to 90 mmHg obtained during three consecutive days. Individuals with controlled hypertension will be those taking antihypertensive medications with either one or two readings of BP less or equal to 140/90. Antihypertensive drugs were classified either as a general category (i.e., antihypertensive drugs) or as a specific group of antihypertensive drugs according to their mode of action (e.g., diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and direct renin inhibitors)

Duration of hypertension: Duration of HTN (in years) was defined as the period beginning when the person became aware of hypertension -- or was diagnosed by a clinician -- until the day on which research begins as evidenced by the participant's medical records and as reported by the participants.

4.2.3. Medical Records

Medical history: Needed details of the individual's medical history were recorded by the registered nurse (RN) of the nursing facility or by the investigator after obtaining the informed consent and release of confidential information from the participant. This medical record provided information on the following areas: (1) hypertension (e.g., awareness, treatment, and controlled); (2) past and present medical and psychiatric conditions classified according to major body systems; (3) current medications; (4) and the most recent

measurements (e.g., BMI, weight, height), and laboratory work (e.g., blood glucose, hematocrit, serum potassium creatinine, calcium, and lipid profile as well as high density lipoprotein cholesterol and low density lipoprotein cholesterol, triglycerides).

4.2.4. Measures of Cognitive reserve (CR)

Premorbid socioeconomic status: Premorbid socioeconomic status or early family environment was assessed through reporting of parents' (i.e., biological, adopted and foster parents or relatives) years of education, types of occupation, and level of income. Premorbid family/parents' economic status was categorized taking into account the family level of income, the parents' occupation according to the U.S Bureau of Labor Statistics, the Consumer Expenditure Survey of the year 1950, and the parent's levels of education: (1) lower middle class (i.e., parents' level of education less than high school, income less than $4,000, and unskilled); (2) middle class (i.e., parents' level of education more than high school, income between $4,000-$10,000, skilled managerial, professional, or technical occupation); (3) upper middle class i.e., parents level of education more than college, family income more than $10,000, a highly skilled managerial, professional, or technical occupation). Standards for 1950 were selected to match the income timeframe of the participants' parents.

Premorbid intelligence/IQ: The estimation of an individual's premorbid intellectual functioning was assessed using the Vocabulary and Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence-Second edition (WASI-II, Wechsler, 2011). Previous studies have used NART (Stern, 2005), Wechsler intelligence scales, and achievement tests (WRAT III). However, Manly and colleagues (2007) have reported that the

use of reading measures (NART and WRAT) as indicators of intelligence to be "controversial" because these tests present some flaws; for example, they assess verbal stimuli which activate mostly the left side of the brain. In this line, this study will use WASI-II, one of the Wechsler intelligence scales, which was designed as a quick and an accurate estimation of a person's intellectual functioning (6-90 years old). This measure can be used as a screening tool to obtain estimates of an IQ score for research purposes (Wechsler, 2011). The two subtests Vocabulary (VOC) and Matrix Reasoning (MR) provide the Full Scale IQ (FSIQ-2) used as a measure for premorbid intellectual functioning. The Vocabulary is a subtest of 31 items (mostly verbal), which requires the examinee to define words, and measures the crystallized intelligence, the fund of knowledge, learning ability, long-term memory, and the degree of language development (Wechsler, 2011). The Matrix Reasoning is a 30-item subtest which requires the examinee to visualize a series of incomplete matrices and complete each one of them by choosing the correct option. This test assesses fluid intelligence, broad visual intelligence, classification, spatial ability, knowledge of part-whole relationships, simultaneous processing, and perceptual organization (Weschler, 2011). WASI-II has excellent psychometric properties with a higher reliability for adults (.93 for FSIQ-2, .85 to .95 for Vocabulary, from .85 to .93 for Matrix Reasoning) and validity (e.g., FSIQ-2 accounts for 72% of WISC-IV FSIQ and 74% of WAIS-IV FSIQ) (Wechsler, 2011). In this study, the FSIQ-2 score was used as the measure of premorbid intellectual functioning while the Vocabulary score was used for crystalized intelligence (reserve) and the Matrix Reasoning score would represent fluid intelligence (reserve).

Education: The level of education was assessed by using the years of education and health literacy. This study used the American educational system (i.e., high school corresponding to at least 12 years of education, college to 16 years, graduate school to more than 16 years). Health Literacy was measured with the Newest Vital Sign (NVS), which has a reliability (Cronbach alpha) of more 0.76 (Weiss, et al., 2008, 2005). This test presents nutrition facts (e.g., fat, cholesterol, sodium, carbohydrate, protein) as well as ingredients and six questions which screen the person's health literacy. Weiss and colleagues (2008, 2005) have suggested a score of 0-1 as a likelihood of limited literacy, a score of 2-3 as indicative of the possibility of limited literacy, and a score of 4-6 as adequate literacy.

Premorbid leisure activities: Leisure activities were assessed by using the Cognitive Activities Scales (Wilson, 2003) and a self-report questionnaire on spirituality/religiousness. The Cognitive Activities Scale (CAS) is a 7-item measure of cognitively stimulating activities (e.g., playing a game, telling a story, visiting a library, reading a newspaper or magazine or book, writing a letter) which assess the frequency of activity on a Likert scale ranged from 1 to 5 (i.e., 1= once a year or less; 2 = several times a year; 3 = several times a month; 4 = several times a week; 5 = every day or nearly every day). This quick assessment of lifetime cognitive activity has a high internal consistency (coefficient alpha= 0.88) and a temporal stability of one month re-test interval of r=.79 (Wilson, et al., 2003). Two new items (i.e., playing musical instruments and doing art) were added into the measure. In this study, the total score of frequencies of activities on the CAS revised was used for leisure activities.

In assessing spirituality and religiousness, this study considered these two concepts as separate and as private and collective experiences and behaviors. In measuring spirituality/religiousness of hypertensive individuals, previous studies have assessed mostly the frequency of prayer (Buck, et al., 2009), attendance at religious services (Bell, et al., 2011; Buck, et al., 2009), and daily spiritual experience (Fitchett, et al., 2009). In the line of cognitive reserve, this study evaluated spirituality and religiousness by measuring the frequency and duration of these activities by using a self-report questionnaire developed by the investigator. In terms of the frequency of activities engaged in privately or socially, this study inquired about daily, weekly, monthly, or yearly participation in spiritual or religious practices. In addition, participants who engaged daily in private or social religious/spiritual practice were required to indicate the frequency (e.g., once, twice, three times or more) and the duration (e.g., 0-10 minutes, 10-20 minutes, 30-40 minutes, 50 minutes or more). This study requested the participants to rate their overall level of spirituality and religiousness as an experience and a behavior. In addition, this study asked participants to indicate how much spirituality and religiousness impact their physical, mental, and behavioral health. Scoring consisted of the total score of all the questions inquiring about the frequency, duration, and self-rating of spirituality/religiousness during the last year.

Occupational attainment: Occupational attainment was assessed using the individual occupational prestige (i.e., the admiration and respect that a particular occupation holds in society independently of the individual occupying it). Occupational prestige was used because the worthiness of an occupation implies average level of income and education. High occupational prestige is often correlated with a high level of education, which in turn requires

a high level of intelligence (Nakao & Treas, 1994, 1998). In this study, occupational prestige was classified using the National Opinion Research Center (NORC, 1989) scores, which rank occupations on a scale of 0 to 100 with 0 as the lowest and 100 as the highest rank (see list of prestige scores). In this study, a female in a religious order was considered as a clergy in terms of occupational prestige.

Physical activity: Physical activity (i.e., any aerobic exercise equal to 30 minutes or more) was measured by the Physical Exercise Questionnaire, which requests the individual's information about physical activity performed in late-life (i.e., within 1 year of the date of testing) and midlife physical activity (i.e., between the ages of 50 and 60). In addition, this questionnaire asked information about whether or not an individual participates in light exercise (e.g., bowling, leisurely walking, stretching, slow dancing, and golfing using a cart), moderate exercise (e.g., brisk walking, hiking, aerobics, weight lifting, strength training, swimming, tennis doubles, yoga, martial arts) and vigorous exercise (e.g., jogging, backpacking, bicycling uphill, tennis singles, racquetball, skiing, and intense use of an exercise machine). Finally, the Physical Exercise Questionnaire uses 6 levels of frequency of exercise (<1 time per month, 2-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, and daily). This test has an internal consistency Cronbach's alpha of 0.71 as well as test-retest correlations of 0.47 for light exercise, 0.50 for moderate exercise, and 0.33 for rigorous exercise (Geda, et al., 2010). Taking into account Geda and colleagues' findings (2010), this study used the frequency of moderate exercise during midlife (i.e., between the ages of 50 and 60) as a proxy of cognitive reserve. In addition, scale-development analyses will be conducted using lifetime frequency.

4.2.5. Neuropsychological Assessment/Cognitive Assessments

Executive functions: Executive functions was measured by the Stroop Color-Word Interference Test and the Design Fluency of Delis-Kaplan Executive Function System (D-KFES, 2001). The D-KEFS Color-Word Interference Test is a test of the examinee's ability to "inhibit over-learned verbal responses" which has two basic conditions (i.e., naming of a color and reading of a color-word), the inhibition condition, and the inhibition/switching condition (Delis, Kaplan, & Kramer, 2001). During the two basic conditions, the examinee was required to name the color and read the words. In the third condition, the examinee was asked to read the color names which were printed in different colored inks. In the last condition, the examinee was requested to read the name of the color of the ink without reading the word. However, when the word was in a box, the examinee was not to read or name the ink color. While the two basic conditions assess the naming speed, conditions 3 and 4 are known to evaluate verbal inhibition and cognitive flexibility which are related to the performance in the first two conditions (Delis, Kaplan, & Kramer, 2001). Scoring consisted in recording the completed time in seconds of each condition (Delis, Kaplan, & Kramer, 2001). This study used the scores of all the four conditions but mostly specially condition 3 and condition 4, which represent respectively two important executive functions (i.e., inhibition and cognitive flexibility). In addition, D-KEFS Design Fluency test is a test of "high executive functioning" that evaluates the examinee's ability to draw many different figures in 60 seconds using four lines that should be connected (Delis, Kaplan, & Kramer, 2001). Unlike the Stroop Color-Word Interference test, this test has three conditions, filled dots, empty dots only, and switching. During the first condition, the examinee was required

to draw the design connecting the dots. The second condition presented the examinee with filled and unfilled dots, and asked the examinee to only connect the unfilled dots to evaluate the examinee's ability of inhibiting what s/he learned in the first condition. In the third condition, the examinee was also presented with unfilled and filled dots but was required to draw designs by connecting filled and unfilled dots. Scoring consisted in the number of correct designs drawn in each condition in 60 seconds (Delis, Kaplan, & Kramer, 2001). Kaplan and colleagues (2001) have indicated that this test measures basic visual attention, motor speed, visual-perceptual skills, and constructional ability as well as executive functions such as initiation of problem-solving behavior, fluency in generating visual patterns, creativity in drawing designs, observations of rules, and inhibition of responses. Schretlen and colleagues (2013) have shown that this test accounts for more than 10% of education variance and less than 5% of variance of IQ. The total score of the three conditions was used in this study to assess different executive functions. The raw scores were converted in scaled scores, which were transformed in T-scores using the conversion table of neuropsychology assessment. Various scored of these measures of executive functions are summarized in Table 27.

Attention: Attention was measured using the Trail Making Test B (TMT; Reitan, 1949), the Digit Span and the Letter-Number Sequencing subtests of the Wechsler Adult Intelligence Scale-Fourth edition (WAIS-IV; Wechsler, 2008). The TMT is a two-part test (A&B) which requires the examinee to connect numbers in sequence with lines as fast as possible (TMT A) and then to alternate numbers and letters following the sequence (TMT B). The TMT B, which measures divided attention, has one-year test-retest reliabilities of .53-.63 for TMT A

and .67-.72 for TMT B in older adults (Strauss, et al., 2006). Schretlen and colleagues (2013) have reported that TMT-B accounts for more than 15% of variance of IQ. Scoring consisted in recording the completion time of each part in seconds. The score of TMT B was used as a measure of visual scanning divided attention in this study. Attention was also assessed by the Digit Span, a subtest of WAIS-IV which consists of Digit Span Forward (i.e., recalling numbers read in the same order), Digit Span Backward (i.e., recalling numbers in reverse order), and Digit Span Sequencing (i. e., recalling numbers and words in ascending order). This subtest, which assesses short-term memory and ability to shift thought patterns, has been used as a measure of concentration and attention (Groth-Marnat, 2009). This subtest has average split-half reliability of .93. The Letter-Number Sequencing subtest of the WAIS-IV was also used to assess attention, auditory short-term memory, sequencing ability, and concentration. This subtest requires the examinee to listen to a sequence of numbers and letters that are read aloud and to recall the numbers in ascending order and the letters in alphabetical order (Wechsler, 2008). This test has good to adequate psychometric properties with a test-retest reliability of .80 and factor loading of 0.69 with the working memory index. The scoring consisted in summing up the numbers of correct items scored (Wechsler, 2008). The raw scores were converted in scaled scores, which were transformed in T-scores using the conversion table of neuropsychology assessment. Various scored of these measures of attention are summarized in Table 27.

Memory: Memory was assessed by two measures, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) and the Rey Complex Figure Test (RCFT; Rey, 1941). The RAVLT is a well-known and often-used measure that has one list of 15 nouns read out loud five times

consecutively and followed by a free recall. After completing the five trials, an interference list B of 15 words was read and followed by free recall. After reading list B, the examinee was tested on a delayed recall of the first list (i.e., the list read five times). The Long Term Memory (LTM) of list A was assessed after a period of 20 minutes. This assessment of LTM was followed by Recognition, which consisted of asking the examinee to identify whether or not a certain word was on the list A (i.e., the list read five times). The score of each trial was the number of correct words remembered. Therefore, this test evaluated immediate memory span, new learning, susceptibility to interference, and recognition (Strauss, et al., 2006). This measure has very good psychometric properties with high internal reliability (coefficient alpha about 0.90) and very good relations within tests (e.g., Delayed-recall scores correlate highly with total score, r >.75) (Strauss, et al., 2006). Studies have indicated that this measure of auditory verbal memory (e.g., the recall) was highly correlated with IQ and education (Vakil et al., 1997 as reported by Strauss, et al., 2006). In this study, the scores of the immediate memory (i.e., the total of the first five trials), LTM, and Recognition were used. Another measure of memory used was the Rey Complex Figure Test (RCFT). The RCFT (Rey 1941) is a measure of visual-spatial constructional ability and visual memory (Strauss, et al., 2006). The RCFT has been found to have good psychometric properties with both alpha split-half and coefficient alpha reliabilities greater than .60 and a high correlation between Immediate Recall and Delayed Recall (r=.88) (Strauss, et al., 2006). Modest correlations have been noted between RCFT and measures of intelligence (IQ) (Boone, et al., 1993 as reported by Strauss, et al., 2006). The test consisted of copying a complex figure from a first trial which was followed by an immediate recall trial after three minutes and

delayed recall of the same complex figure after 30 minutes. After the delayed recall, the examinee was required to identify among different parts those which were parts of the complex figure presented and drawn. Scoring criteria consisted in the accuracy and the placement of each part drawn in the complex figure. The scores for immediate visual memory (i.e., score for immediate recall), long-term visual memory (i.e., score for delayed recall) and recognition were used in this study. Various scored of these measures of memory functions are summarized in Table 27.

Language: Language was assessed by the verbal fluency test, FAS and Animals test. This verbal fluency test required the examinee to name in 60 seconds words that start with F, A, and S with exception of proper names and words with the same suffix. The second part of this test requested the examinee to name animals in 60 seconds. Schretlen and colleagues (2013) have shown that this test accounts for almost 20% of variance of IQ. Scoring consisted in counting the total numbers of words produced by the examinee which start with the word F, A, S and the number of animals named after the completed time. In this study, the total score of FAS and Animals was used as measures of verbal fluency. Various scored of these measures of verbal fluency are summarized in Table 27.

Speed of information processing: Processing speed was measured with the Coding subtest of the WAIS-IV and TMT A. This 120-second subtest required the examinee to mark in the empty box the number which corresponds to the shape. This subtest, which correlates with FSIQ of the WAIS-IV (.59), assesses psychomotor speed, clerical speed, and accuracy. Scoring this subtest consisted in counting the number of correctly completed items within the time limit (Wechsler, 2008). The score of TMT A has been used as measure of the speed of

information processing (Heaton, et al., 2004). The raw scores of the Coding subtests were converted in scaled scores, which were transformed in T-scores using the conversion table of neuropsychology assessment.

Visuospatial skills: Visual spatial abilities was assessed by using the Block Design (BD) subtest of the WAIS-IV and the score of RCFT-copy (see Memory above). This test, which highly correlates with general IQ (.66 with FSIQ of WAIS-IV), measures spatial visualization, visual spatial-motor-spatial coordination, perceptual organization, perceptual speed, abstract conceptualization, and visuomotor coordination (Groth-Marnat, 2009). This subtest required the examinee to work within a specified time limit in order to re-create a design viewed by using red-and-white blocks (Wechsler, 2008). Scoring consisted in calculating the total of the design correctly constructed within the time limit. The RCFT-copy was also used as a measure of visual spatial abilities. The raw scores of the BD were converted in scaled scores, which were transformed in T-scores using the conversion table of neuropsychology assessment. Various scored of these measures of attention were summarized in Table 27.

4.3. Procedures

The primary investigator called the religious superiors or directors of nursing homes or living communities and pastors of different parishes to arrange a meeting. An initial meeting was held with Religious superiors or directors of nursing homes or the pastor to inform them about the research project and to request volunteers from among their members to participate in this study. After meeting with religious superiors or directors or pastors, another meeting was conducted with the head nurse of each nursing home or residence or

parish to request their help and their availability to commit to this research. For example, the registered nurse helped in providing medical records, medical history, measuring blood pressure, height, weight, BMI and providing some lab results. In the case of parishes, an announcement was made after the end of the mass requesting volunteers and the place of meeting was also indicated in the announcement. Interested participants attended an orientation session conducted by the primary investigator explaining in details the research project, the requirement, the informed consent, and release of confidential information. At this time, all interested participants completed the informed consent form, release of their medical records, received a number to identify them, and chose an individual time to be assessed at their retirement house or in one of the parish offices. Participants from the parish were informed that three readings of their blood pressure would be taken every Sunday after their usual mass by a parish registered nurse. These participants also signed the authorization of release of confidential information in order to request their primary care physicians to send their laboratory works (e.g., electrolytes, lipid, and some chemistry results) to the primary investigator. After this orientation meeting, the primary investigator administered the self-report measures to participants and filled out medical record for participants who were from the parishes. Finally, graduate students trained in neuropsychological assessments also conducted individual neuropsychological evaluations. These neuropsychological assessments were given in a room designated by the religious superiors or directors of the nursing home or residence or by the pastors. Each participant was informed by the nurse about the room designated for the assessment and one's specific time for cognitive

evaluation. All the participants will be assessed following the same sequence of neuropsychological assessment.

4.4. Power Analysis for Sample

A power analysis was conducted to estimate sample size model in this investigation. Kadzin (2003) has suggested the power of an investigation to be related to alpha level (0.05), effect size (ES=0.8), and sample size. Cohen (1998) considered .80 as a large ES, 0.50 as a medium ES, and 0.20 as a small. A literature review of previous studies has found that the effect size of hypertension on different cognitive functions varied between small and large. For example, there was a range of effect size between small to large for executive functions (0.26-0.92), memory (0.21-0.96), processing speed (0.2-1.00) and spatial ability (0.18-0. 79) as well as a range of small (0.01) to medium (0.6) for attention and a small effect size for language. The effect size of hypertension on cognitive function can be approximately estimated as being on the medium level.

Using the G-Power 3.1.3 program, the power of the sample was estimated considering the two-tailed, alpha level of 0.05, power of 0.80, and medium effect size (0.5) of hypertension on cognitive function. Using the Multivariate Analysis of Variance (MANOVA), a sample size of 128 participants was found as required to find a difference when comparing groups of hypertensive and normotensive. In addition, a sample of 82 participants was found to be needed for conducting a Pearson correlation. Using a linear multiple regression with four predictors (i.e., hypertension, antihypertensive, cognitive reserve, and covariate), a sample size of at least 99 participants was calculated to detect a medium-sized effect of these predictors on the dependent variable (i.e., cognitive functions).

Based upon this range of requirements from different statistical methods, we proposed to use the highest number (i.e., 128 participants) in this study in order to find sufficient power to detect a difference.

CHAPTER 5: RESULTS

This section will present the demographic and medical information as well as analyses of cognitive reserve and cognitive function data. In addition, this section will describe the results of hypothesis tests and of secondary analyses.

5.1. Demographic and Medical Information, Cognitive Reserve and Functions

5.1.1. Demographic Characteristics of the Sample

The sample included 150 individuals[1], which included 82 male (55%) and 67 female (45%). This sample was mostly comprised of 123 Caucasians (83%), followed by 14 Blacks (9%) and few of other ethnic groups. In terms of status, 81 participants were priests and nuns or consecrated (54%) from seven religious congregations, and 68 participants were lay (46%) from three parishes of the archdiocese of Detroit. The religious order participants included 22 Jesuits (15%), 19 Sisters of Immaculate Heart of Mary (13%), 12 Felician Sisters (8%), 10 of the Society of Divine Word (7%), 8 Sisters of Mercy (5%), 7 Holy Spirit Sisters (5%), and 2 priests of the Archdiocese of Detroit. These data were collected from 12 different locations, mostly Detroit, Michigan and Chicago, Illinois (See Table 12).

Table 12: Demographic Characteristics of the Sample (N=149)

Characteristics	N	%
Age		
45-49	8	5
50-59	24	16
60-69	34	23

[1] Although the sample included 150 participants, two or three participants will have some of their data missing. Therefore, the number will vary beween 147 to 149 participants in different analyses.

70-79	25	17
80-89	43	29
90-99	15	10
Gender		
Male	82	55
Female	67	45
Ethnicity		
Caucasian	123	83
Black	14	9
Indian American	3	2
Hispanic	3	2
Native Hawaiian	3	2
Asian American	2	1
Other	1	1
Status		
Priests and nuns	81	54
Lay	68	46
Religion		
Christianity	146	98
Hinduism	1	1
No religion	2	1
Religious Status		
Lay	70	47
Society of Jesus (SJ)	22	15
Immaculate Heart of Mary (IHM)	19	13
Felician Sisters (CSSF)	12	8
Society of the Divine Word (SVD)	10	7
Sisters of Mercy (RSM)	8	5
Holy Spirit Sisters (SSPS)	7	5
Archdiocese of Detroit	2	1
Location		
St. Mary Parish: Royal Oak, Michigan	36	24
Immaculate Heart of Mary: Monroe, Michigan	19	13
Felician Sisters: Livonia, Michigan	14	9
Jesuit Colombiere Center: Clarkston, Michigan	11	7
Gesu Parish: Detroit, Michigan	11	7
University of Detroit Mercy: Detroit, Michigan	11	7
SVD: Techny, Illinois	10	7

Holy Spirit Sisters: Chicago, Illinois	10	7
St. Peter Clever Parish: Detroit, Michigan	10	7
Jesuit Lansing Reilly Hall: Detroit, Michigan	9	6
McAuley Center: Farmington Hills, Michigan	7	5
Senior Clergy Retirement Village: Livonia, Michigan	3	2
Father		
Deceased	122	85
Living	20	14
Unknown	1	1
Mother		
Deceased	125	86
Living	20	14
Unknown	1	1

Table 12b:
Other Demographic Characteristics of the Sample

Characteristics	M	SD
Age at time of survey (years)	72.5	13.7
Number of jobs during lifetime	6.03	3.88
Number of languages spoken	1.41	0.65
Siblings	3.67	2.5
Step-siblings	0.09	0.49
Half-siblings	0.18	0.68
Mother's age at time of death	79.2	12.3
Father's age at time of death	73.5	15.3
Score of MMSE	28.6	1.4

5.1.2. Behavioral Health Measures

Participants obtained an average score of 2.83 (SD=3.00) in PHQ-9 and of 1.92 (2.95) in GAD-7. These low scores in PH-9 and GAD-7 indicate either that participants denied endorsing any symptoms of depression and anxiety or did not have them. Participants rated the intensity of cognitive functions, averaging 45.55 (SD=49.58) on the total score of the SC and less than less 3 on each cognitive function (on a scale of 0 to 10). The highest of the

generally low scores were on chronic pain and anxiety symptoms. These low scores also show that participants did not report any neuropsychological deficits at the time of testing. The results of behavioral measures and self-report of neuropsychological symptoms are summarized in the following table (see Table 13).

Table 13: Behavioral Health Measures (N = 149)

Neuropsychological Symptom	M	SD
Patient Health Questionnaire total	2.83	3.00
Anosognosia (in denial of a problem) (0-10)	0.86	1.74
Anxiety (0-10)	2.15	2.32
Attention deficits - easily distractible (0-10)	2.02	2.40
Auditory sequencing problems (0-10)	1.38	2.23
Balance problems (0-10)	2.04	2.64
Blurred vision (0-10)	1.40	2.28
Chronic pain (0-10)	2.21	2.94
Compulsive behaviors and/or thoughts (0-10)	1.20	1.88
Concentration problems (0-10)	1.81	2.03
Decreased tactile or skin sensitivity (0-10)	0.80	1.74
Delusional (0-10)	0.19	0.88
Depression (sad & blue) (0-10)	1.18	1.99
Difficulty comprehending social cues (0-10)	0.82	1.55
Dyscalculia - problems calculating (0-10)	1.02	1.95
Dyslexia - letter reversal (0-10)	0.46	1.44
Executive function problems (0-10)	0.71	1.72
Face recognition problems (0-10)	1.02	2.12
Failure to initialize Actions (0-10)	1.13	1.82
Hyperactive and/or agitation (0-10)	0.88	1.49
Impulsive behaviors (0-10)	0.81	1.47
Insensitive to other's emotional expressions (0-10)	0.97	1.59
Insensitive to other's feelings (0-10)	0.93	1.57
Low motivation (0-10)	1.58	1.94
Low threshold for anger & loss of control (0-10)	1.07	1.68
Migraine headaches (0-10)	0.43	1.61
Mood swings (0-10)	0.81	1.53
Multi-tasking problems (0-10)	1.23	1.76

Obsessive thoughts about self (0-10)	0.87	1.70
Obsessive thoughts and/or hyper-focused (0-10)	0.68	1.47
Oppositional defiant conduct (0-10)	0.45	1.11
Orientation in space problems (0-10)	0.57	1.34
Perception of letters problems (0-10)	0.48	1.41
Poor judgment (0-10)	0.78	1.35
Poor skilled motor movements (0-10)	1.05	1.65
Poor social skills (0-10)	0.89	1.52
Receptive language problems (0-10)	0.66	1.56
Recognizing objects by touch problems (0-10)	0.50	1.18
Self-esteem problems (0-10)	1.32	1.93
Sequential planning problems (0-10)	0.62	1.24
Short-term memory problems (0-10)	2.03	2.24
Slow reader (0-10)	1.45	2.23
Slowness of thought - easily confused (0-10)	0.90	1.64
Spatial perception problems (0-10)	0.54	1.28
Speech articulation problems (0-10)	0.83	1.41
Symptoms of fibromyalgia (0-10)	0.44	1.51
Word finding problems (0-10)	1.42	1.94
Symptom Checklist total score	45.55	49.58
Generalized Anxiety Disorder Assessment (GAD 7)	1.92	2.95

5.1.3. Medical Record Data

5.1.3.1. Blood Pressure

This study included 58 normotensive (39% of the sample) and 90 hypertensive participants (61%). All the participants with hypertension were aware of and treated for their hypertension. Majority of those with hypertensive had their hypertension controlled. Descriptive statistics of participants' blood pressure indicated that all participants had on average three normal readings of systolic and diastolic of their blood pressure (See

Table 14).

Table 14: Participant Blood Pressure Characteristics (N=148)

Characteristic	N	%	% of HTN
Blood Pressure			
Normotensive	58	39	
Hypertension	90	61	
Awareness of hypertension	90	61	100
Treatment of hypertension	90	61	100
Controlled hypertension	68	45	76
Uncontrolled hypertension	22	17	24

Two different durations of hypertension were provided. The first one was provided from the medical record by the RN and the second was reported by the participant. The duration of hypertension provided by the RN included only 42 participants out of 90 participants with hypertension of which 21 participants had 10 years or less (23.3 % of the hypertensives) and 21 with more than 10 years (23.3 % of the hypertensives). The second duration of hypertension provided by the participants had an average duration of 13.66 years of hypertension (SD=14.41). In this category, 62 participants of 90 hypertensive participants reported their duration of hypertension of which 25 individuals had hypertension for a duration of 10 years or less (28 % of the hypertensives) and 37 for more than 10 years (41 % of the hypertensives). These participants had an average duration of hypertension of 7.19 years (SD=12.47) (See

Table 15). In this study, the duration of hypertension data provided by the participants was used for statistical analyses due to its bigger sample than the one provided the RN.

Table 15: Reported Duration of Hypertension

Characteristic	N	%	% of HTN
Duration of hypertension in years (given by participant)			
10 years or less	25	21	28
More than 10 years	37	32	41
Duration of hypertension in years (given by the nurse)			
10 years or less	21	24	23
More than 10 years	21	24	23

Table 16: Participant-reported Duration of Hypertension

Characteristic	M	SD
Duration of hypertension		
Duration of hypertension in years (given by participant)	7.19	12.47
Duration of hypertension in years (given by the nurse)	13.66	14.41

Concerning antihypertensive drugs, participants were mostly treated with Beta Blockers (43 participants, 48 % of hypertensives) followed by Angiotensin Converting Enzyme (35 participants, 39% of hypertensives), Diurectics (26 participants, 29% of hypertensives), Calcium Channel Blockers (23 individuals, 26 % of hypertensives), and Angiotensin Receptor Blockers (19 participants, 21% of hypertensives), Vasodilators (15 participants, 17 % of hypertensives), two antihypertensives combined (32 participants, 36% of hypertensives), three combined antihypertensives (14 participants, 16 % of hypertensives), and four combined antihypertensives (5 participants, 16 % of hypertensives) (See

Table 17). As noted above, among 90 participants with hypertension, 68 had their hypertension controlled (75% of treated hypertensives) and 22 had uncontrolled hypertension (25% of treated hypertensives) (see

Table 17).

Table 17. Hypertension Medications

Characteristic	N	%	% of HTN
Hypertension medications			
Beta blockers (BBs)	43	30	48
Angiotensin converting enzyme (ACEIs)	35	24	39
Combined two drugs	32	22	36
Diuretics	26	18	29
Calcium channel blockers (CCBs)	23	16	26
Angiotensin Receptor Blockers (ARBs)	19	13	21
Vasodilators	15	10	17
Combined three drugs	14	10	16
Combined four or more drugs	5	3	6

5.1.3.2. Medical History

Participants in this study had an average height of 169.22 cm (5’6’’, SD=15.33) and average weight 76.77kg (168 pounds, SD=19.01). They were slightly overweight with a Body Mass Index of 26.81 (SD=6.39) (See

Table 18). In terms of their hours of sleep per night, 87 (59% of the sample) slept on an average of 7 to 8 hours, 46 individuals for 5 to 6 hours, and 12 for more than 8 hours, and only 2 for 0 to 4 hours per night. Regarding their habits, 35 participants were involved in taking ketamine, 20 individuals smoked tobacco, 17 drank alcohol and 4 were recovering alcoholics. Sixteen participants had received hormone therapy, 11 radiation, 7 chemotherapy or cardiac transplantation (See

Table 18).

Their laboratory results in general show normal findings with some decrease of the level of chloride (90.23, SD=34.19) and some elevations in High Density Lipoprotein (HDL) cholesterol (51.59, SD=27.68) (See

Table 18).

Table 18: Medical information (N=148)

Characteristic	M	SD
Height	169.22	15.33
Weight	76.77	19.01
Body Mass Index (BMI)	26.81	6.39
Blood Glucose	99.58	47.45
Hematocrit	37.96	14.42
Creatinine	0.92	0.37
Sodium	134.35	27.13
Potassium	5.38	10.35
Calcium	8.12	3.07
Chloride	90.23	34.19
Serum potassium	5.39	12.48
Lipid	154.98	70.89
HDL	51.59	27.68
LDL	89.80	41.65
Triglycerides	118.13	72.87
Thyroid	1.35	1.19
Number of medical diagnosis	5.61	6.40
Number of psychiatric diagnosis	0.22	0.53
Number of medications	7.94	6.71
Characteristic	N	%
Hours of sleep		
0 to 4	2	1
5 to 6	46	31
7 to 8	87	59
More than 8	12	8
Other factors		
Ketamine	35	24
Tobacco	20	14
Alcohol	17	12
Hormone therapy	16	11
Radiation	11	8
Chemotherapy	7	5
Cardiac transplant	7	5
Recovering alcoholic	4	3
Opiates	4	3

Carotid	3	2
Amphetamine	2	1

Contrasting laboratory findings between normotensive (n=58) and hypertensive (n=90), hypertensive participants had some slight elevations in the value of hematocrit (38.80, SD=15.11 vs 35.99, SD=12.71), creatinine (0.97, SD=0.32 vs 0.79, SD=0.45), sodium (139.52, SD=2.65 vs 122.08, SD=47.83), calcium (8.56, SD=2.48 vs 7.15, SD=3.95), and chloride (93.49, SD=29.21 vs 81.37, SD=44.35). There was higher value of triglycerides among hypertensive participants (131.03 SD=76.95) compared to normotensives (92.48, SD=56.43). In terms of cholesterol, hypertensive individuals had lower values than normotensive of lipid (147.89, SD=67.33 vs 168.89, SD=76.82), HDL (48.97, SD=26.80 vs 57.52, SD=29.35 but higher LDL (86.68, SD=38.55) than normotensive (96.40, SD=48.10) (See Table 19). Table 19 shows a comparison of some health issues between normotensive and hypertensive participants.

Table 19: Comparison of Health Issues Between Normotensive and Hypertensive Participants (N = 147)

	Normotensive					Hypertensive				
Characteristic	M	SD	Median	95%cl	Range	M	SD	Median	95%cl	Range
Height	167.53	10.34	167.64	[164.79,170.28]	53.00	170.29	17.75	168.00	[166.57,174.01]	150.90
Weight	72.30	20.32	69.00	[66.91,77.69]	132.00	79.60	17.67	78.02	[75.89,83.30]	71.53
BMI	26.19	6.37	25.50	[24.49,27.90]	36.90	27.19	6.41	26.30	[25.84,28.54]	34.00
Glucose	98.96	71.90	87.00	[73.04,124.89]	479.15	99.58	30.71	94.00	[92.09,107.07]	257.00
Hematocrit	35.99	12.71	40.65	[31.06,40.92]	46.50	38.80	15.11	40.00	[35.06,42.55]	127.00
Creatinine	0.79	0.45	0.80	[0.62,0.97]	1.86	0.97	0.32	0.90	[0.89,1.04]	1.90
Sodium	122.08	47.83	140.00	[104.54,139.63]	145.00	139.52	2.65	140.00	[138.89,140.14]	12.00
Potassium	7.04	18.06	4.40	[0.42,13.67]	104.00	4.68	4.00	4.20	[3.74,5.62]	34.40
Calcium	7.15	3.95	9.10	[5.70,8.60]	10.00	8.56	2.48	9.20	[7.96,9.17]	10.60
Chloride	81.37	44.35	104.00	[63.82,98.91]	108.00	93.49	29.21	103.00	[86.47,100.50]	110.00
Lipid	168.89	76.82	184.00	[138.50,199.28]	265.00	147.89	67.33	158.00	[129.33,166.44]	255.00
HDL	57.52	29.35	60.00	[47.11,67.92]	123.00	48.97	26.80	46.00	[42.58,55.36]	200.00
LDL	96.40	48.10	101.00	[79.35,113.45]	166.00	86.68	38.55	89.20	[77.49,95.87]	172.00
Triglycerides	92.48	56.43	87.00	[72.47,112.50]	202.00	131.03	76.95	123.00	[112.68,149.38]	521.00
Number of Medical Diagnoses	2.72	3.19	2.00	[1.87,3.57]	13.00	7.43	7.21	5.50	[5.92,8.94]	51.00
Number of Psychiatric Diagnoses	0.16	0.56	0.00	[0.01,0.31]	3.00	0.26	0.51	0.00	[0.15,0.37]	2.00
Number of Medications	4.30	5.75	3.00	[2.76,5.84]	27.00	10.20	6.27	9.50	[8.89,11.51]	32.00
Thyroid	1.19	1.33	0.69	[0.58,1.79]	4.38	1.40	1.13	1.43	[1.08,1.73]	4.02

Participants with uncontrolled hypertension showed some elevations in the three systolic readings compared to participants with controlled hypertension (148.41, 148.09, and 149.50 vs 125.72, 125.36, and 125.98). This suggests that participants in this sample had uncontrolled systolic hypertension rather than diastolic hypertension. In addition, there were some light elevations in values such as BMI (27.32, SD=8.32 vs 26.77, SD=5.73), hematocrit (40.02, SD=4.31 vs 38.64, SD=16.60), calcium (9.32, SD=0.50 vs 8.41, SD=2.71), and chloride (97.83, SD=24.75 vs 93.14, SD=29.52). In addition, participants with uncontrolled hypertension presented high values compared to participants with controlled hypertension in all the types of cholesterol: lipid (162.60, SD=53.17 vs 146.05, SD=73.48), HDL (55.69, SD=17.35 vs 48.32, SD=29.16), and LDL (101.31, SD=27.30 vs 85.53, SD=41.74). There was higher elevation of triglycerides among participants with uncontrolled hypertension (164.00, SD=106.24) compared to those with controlled hypertension (121.54, SD=62.88) (see Table 20). Table 20 shows a comparison of some health issues between those with controlled (n=68) versus uncontrolled (n=22) hypertension.

Table 20: Comparison of Health Issues Between Participants with Controlled Versus Uncontrolled Hypertension (N = 148)

	Controlled					Uncontrolled				
Characteristic	M	SD	Median	95%cl	Range	M	SD	Median	95%cl	Range
Height	170.06	19.43	167.82	[165.36,174.76]	150.90	167.88	10.35	169.00	[163.30,172.47]	36.00
Weight	78.59	16.26	77.56	[74.65,82.53]	68.18	76.42	21.72	75.33	[66.79,86.05]	74.93
BMI	26.77	5.73	25.60	[25.37,28.16]	28.20	27.32	8.32	25.70	[23.63,31.01]	33.00
Systolic - first day	125.72	12.93	126.00	[122.59,128.85]	70.00	148.41	11.11	146.00	[143.48,153.33]	50.00
Systolic - second day	125.36	12.90	128.00	[122.21,128.51]	73.00	148.09	13.43	144.50	[142.13,154.05]	56.00
Systolic - third day	125.98	12.04	129.00	[123.00,128.97]	60.00	149.50	13.22	143.00	[143.64,155.36]	39.00
Diastolic - first day	70.53	9.82	70.00	[68.15,72.91]	42.00	77.05	8.90	78.50	[73.1,80.99]	44.00
Diastolic - second day	70.18	12.57	70.00	[67.11,73.24]	94.00	78.05	8.53	79.50	[74.26,81.83]	34.00
Diastolic - third day	70.42	8.77	70.00	[68.24,72.59]	40.00	76.95	8.12	75.50	[73.36,80.55]	35.00
Glucose	99.96	33.09	94.00	[91.10,108.83]	257.00	96.93	12.63	94.00	[89.94,103.93]	49.00
Hematocrit	38.64	16.60	40.40	[34.07,43.22]	127.00	40.02	4.31	40.45	[37.72,42.32]	16.30
Creatinine	0.97	0.35	0.90	[0.88,1.06]	1.90	0.87	0.21	0.87	[0.76,0.99]	0.80
Sodium	139.50	2.73	140.00	[138.80,140.20]	12.00	139.58	2.16	140.10	[138.43,140.72]	7.00
Potassium	6.44	13.53	4.20	[2.95,9.94]	100.40	4.09	0.38	4.15	[3.89,4.29]	1.47
Calcium	8.41	2.71	9.20	[7.68,9.15]	10.10	9.32	0.50	9.20	[9.07,9.58]	2.20
Chloride	93.14	29.52	103.00	[85.38,100.90]	109.00	97.83	24.75	103.70	[84.13,111.54]	101.20
Lipid	146.05	73.48	154.00	[122.23,169.87]	255.00	162.60	53.17	180.00	[133.15,192.05]	223.00
HDL	48.32	29.16	44.50	[40.51,56.13]	200.00	55.69	17.35	54.50	[46.44,64.93]	55.00
LDL	85.53	41.74	88.20	[74.35,96.71]	172.00	101.31	27.30	104.50	[86.77,115.86]	89.00
Triglycerides	121.54	62.88	120.00	[104.70,138.38]	323.00	164.00	106.24	151.50	[107.39,220.61]	478.00
Thyroid	1.42	1.18	1.23	[1.04,1.80]	4.02	1.30	0.90	1.50	[0.73,1.87]	2.90
Number of Medical Diagnoses	7.07	5.20	6.00	[5.82,8.33]	30.00	9.32	11.37	4.00	[4.28,14.36]	51.00

Number of Psychiatric Diagnoses	0.18	0.42	0.00	[0.08,0.28]	2.00	0.41	0.59	0.00	[0.15,0.67]	2.00
Number of Medications	9.99	5.66	9.00	[8.61,11.36]	27.00	10.50	8.13	9.00	[6.90,14.10]	32.00

Information from medical records portrayed a sample with an average of 5.61 medical diagnoses (SD=6.40) (See Table 19), with normotensive participants having on average 2.72 medical diagnoses (SD=3.19) and hypertensive individuals with 7.43 medical diagnoses (7.43, SD=7.21); participants with controlled hypertension had 7.07 (SD=5.20) and individuals with uncontrolled hypertension had 9.32 (SD= 11.37) medical diagnoses. In terms of psychiatric diagnoses, participants were diagnosed on average with 0.22 psychiatric conditions (SD=0.53), of which a normotensive subject had 0.16 (SD=0.56) and participants with hypertension had 0.26 psychiatric conditions; while those with controlled hypertension were diagnosed had 0.18 (SD=0.42) and those with uncontrolled hypertension with 0.41 psychiatric issues (See Table 19 and Table 20).

The overall picture of diseases according to major bodily systems shows a high prevalence of cardiovascular diseases (92 participants) followed predominantly by gastrointestinal (51 participants), orthopedics (46 participants), endocrine conditions (37 participants), neurological issues (36 participants), eye, ear, nose, and throat (EENT) conditions (36 participants). In addition, 36 individuals were recorded with hyperlipidemia, 31 with hypercholesterimia, 25 with diabetic mellitus, 15 with Vitamin B12 deficiency and anemia, 5 with obesity, and 4 with depression and/or bipolar disorder (see

Table 21). Table 21 shows the classifications of participants' diseases.

Table 21: Classifications of Participants' Diseases (N=148)

Body System	N	%
Cardiovascular	92	63
Gastrointestinal	51	35
Orthopedics	46	32
Endocrine	37	26

Neurology	36	25
Hyperlipidemia	36	25
Eye, ear, nose, and throat	34	23
Obstetrics / Gynecology	34	23
Hypercholesterolemia	31	21
Respiratory	28	19
Rheumatology	26	18
Psychiatry	25	17
Diabetic mellitus	25	17
Vitamin B12 deficiency and anemia	15	10
Miscellaneous	14	10
Hematology	8	6
Obesity	5	3
Stroke and ischemic events	5	3
Depression and bipolar	4	3
Urology	3	2
Dermatology	2	1
Dementia	1	1

In terms of medications, participants were treated with an average of 7.94 medications (SD=6.71) with normotensive individuals being treated with 4.30 (SD= 5.75) and hypertensive individuals with 10.20 (SD=6.27). Comparing individuals with hypertension, those with controlled hypertension were treated with an average of 9.99 drugs (SD=5.66) while those with uncontrolled hypertension were taking 10.50 drugs on average (SD=8.13) (See Table 19 and Table 20).

Medications were classified by the primary investigator according to the Nursing Drug Handbook (---, 2011) or the body system they were treating. Participants were mostly treated with antihypertensive drugs (87 participants) followed by dyslipidemia drugs (78 participants), calcium/vitamin D drugs (68 participants), hematologic drugs (52 participants), antiplatelet drugs

(46 participants), and antacids (40 participants). The list of all medications is reported in the following table (See Table 22).

Table 22: Classifications of Participants' Medications (N=148)

Medication	N	%
Antihypertensive	87	60
Dyslipidemia	78	54
Calcium/vitamin D	68	47
Hematologic	52	36
Antiplatelets	46	32
Antacids	40	28
Miscellaneous drugs	33	23
Antihistamines	32	22
Hypothyroidism	32	22
Ophthalmic and nasal drugs	30	21
Diabetic drugs	27	19
Laxatives	26	18
Non-opioid analgesics and antipyretics	24	17
Other GI drugs	23	16
Antidepressants	21	15
Musculoskeletal drugs	20	14
Rheumatologic	19	13
Nonsteroidal anti-inflammatories	16	11
Anti-infectives	15	10
Insomnia drugs	13	9
Calcium disorders	12	8
Corticosteroids	11	8
Anticoagulants	10	7
Short acting beta agonists (SABA)	9	6
Anxiolytics	7	5
Anti-inflammatory	7	5
Benzodiazepines	7	5
Dermatologic	6	4
Bronchodilators	6	4
Alzheimer's disease drugs	6	4
Antianginals	5	3
Other pulmonary drugs	5	3

Anticonvulsants	5	3
Antidiarrheals	4	3
Other hormonal drugs	4	3
Other psychiatric drugs	4	3
Inhaled anticholinergics	3	2
Hyperthyroidism drugs	3	2
Other cardiovascular drugs	2	1
Irritable bowel drugs	2	1
Androgens	2	1
Antiarrhythmics	1	1

In terms of family history of hypertension, 76 participants had one of their parents with hypertension and 55 participants had one of their siblings with hypertension. Concerning environmental factors, many participants reported that they were involved in sodium reduction (68 participants, 76 % of hypertensives) and in increased physical activity (64 participants, 71% of the hypertensives) followed by 50 in potassium supplement intake (56% of the hypertensives), 49 in weight reduction (54 % of the hypertensives), 40 in diet intake (44 % of the hypertensives), 40 in lowering lipid (44 % of the hypertensives), 36 in dietary approaches to stop hypertension (40 % of the hypertensives), and 32 in alcohol moderation (36 % of the hypertensives (See Table 23).

Table 23: Hypertension Risk Factors in the Sample (N=147)

Characteristic	*n*	%	*% of HTN*
Family History of Hypertension			
Parent with hypertension	76	52	
Sibling with hypertension	55	38	
Environmental Factors of Hypertension			
Caffeinated beverages	76	51	84
Sodium reduction	68	46	76
Increased physical activity	64	43	71

Potassium supplement	50	34	56
Weight reduction	49	33	54
Diet	40	27	44
Lipid lowering	40	27	44
Metabolic syndrome	38	26	42
Dietary approaches to stop hypertension (DASH)	36	24	40
Alcohol moderation	32	22	36
Tobacco use	23	16	26
Marijuana	8	5	9
Cocaine	3	2	3

5.1.4. Cognitive Reserve

Concerning early family antecedents as a context for cognitive reserve (CR) of the participants, 70 individuals reported that they came from a middle class family (48%), 57 from lower middle class (39%), and 18 from upper middle class (12%). One hundred and thirteen participants indicated that the quality of their living accommodations were average (78%) while 25 participants reported high quality of living accommodations. In addition, 82 individuals had adequate family income (56%), 23 came from a family with pretty good income (16%), 36 from poor families but with enough money (25%), and 5 from poor families (3%) (See Table 24).

With regard to the level of education of parents/caregivers, 43 participants reported that their father's level of education was elementary school (30%), 25 had fathers who attended college/undergraduate (17%) and the fathers of 24 participants had high-school level of education (16%). Forty-five participants reported that their mothers/caregivers had a high school level of education (31%), 35 individuals whose mothers/caregivers attended elementary school (24 %) and 24 participants had mother/caregivers who had a technical/community college degree (17 %). The majority of the participants (117 participants, 79%) spoke one language at home

(English) while 26 participants (18%) spoke two languages (English and one other language). One hundred and seventeen reported that they had strong parental encouragement for learning and formal education (80% of the sample), 25 participants had adequate encouragement (17%) and 4 had weak support (3%) (See Table 24).

Table 24: Early Family Antecedents of Cognitive Reserve (N=148)

Antecedents of Cognitive Reserve	N	%
Language spoken at home		
English	117	79
English and one other	26	18
English and other languages	3	2
Other than English	2	1
Family situation		
Poor	5	3
Poor but enough	36	25
Adequate	82	56
Pretty good	23	16
Well off	1	1
Parents' socioeconomic status		
Lower middle class	57	39
Middle class	70	48
Upper middle class	18	12
Father's level of education		
Elementary	43	30
Middle / Junior High	15	10
High School	24	16
Technical / Community College	16	11
College / Undergraduate	25	17
Masters	2	1
Graduate	7	5
Don't know	13	9
Mother's or primary caregiver's level of education		
Elementary	35	24
Middle / Junior High	14	10
High School	45	31

Technical / Community College	24	17
College / Undergraduate	14	10
Masters	3	2
Graduate	1	1
Don't Know	9	6
Quality of living accommodations		
High Average	25	17
Average	113	78
Low Average	7	5
Father's health		
Serious health problems	54	37
No major health problems	81	56
Don't know	10	7
Mother's or primary caregiver's health		
Serious health problems	46	32
No major health problems	95	66
Don't know	4	3
Parent’s encouragement of learning and for education		
Strong	117	80
Adequate	25	17
Weak	4	3
Don't know	1	1

Concerning other predictors of CR, participants obtained an average raw score of Full Scale IQ of 118.43 (SD=16.46), which is classified clinically as above average score (FSIQ-2 WASI-II t-score: 115.89, SD=14.28) when compared with individuals of their age. The crystalized intelligence score (WASI-II Vocabulary raw score: 46.02, SD=5.74; T-score: 64.57, SD=10.30) was higher than fluid intelligence (WASI-II Matrix Reasoning raw score: 16.94, SD=4.93; t-score: 53.83, SD=9.70) (See

Table 26). In terms of participants' years of formal education, participants of this study were highly educated with an average of 18.97 years of education (SD=4.09) with 64 reporting to have completed masters' degree (43% of the sample), 46 completed college/undergraduate (31% of the sample), and 29 completed graduate school (20% of the sample) (See Table 25). Forty-seven participants obtained their degree in liberal arts (32% of the sample), 29 in education (20% of the sample), 16 in medicine/health professions (11% of the sample), 16 in business administration (11 % of the sample), and 10 in science (natural and social science: 7% of the sample) (See Table 25). This sample obtained an average score of 4.27 (SD=1.83) in the Newest Vital Sign (NVS), which indicated adequate health literacy.

Table 25: Socioeconomic Characteristics of Participants (N=148)

Characteristics	N	%
Highest education		
Middle/Junior High	1	1
Completed High School	4	3
Completed Technical School / Community College	4	3
Completed College / Undergraduate	46	31
Completed Masters	64	43
Completed graduate school	29	20
Area of education		
Liberal Arts	47	32
Education	29	20
Medicine / Health Professions	16	11
Business	16	11
Other	15	10
Science (Natural and Social)	10	7
Fine Arts	6	4
Law	4	3
Engineering	3	2
Category of occupation		
Managerial	130	88
Semi-skilled	17	12

Salary		
Less than 15,000	32	24
16,000 to 30,000	21	16
30,001 to 80,000	65	49
80,001 to 100,000	11	8
100,001 to 250,000	4	3
More than 250,000	1	1

Participants obtained an average score of 80.80 (SD=17.73) and 101.88 (SD=23.18) in the revised version of the Cognitive Activities Scale (CAS) (See

Table 26). Cognitive activities increased from age 6 (15.75, SD=4.43), 12 (21.06, SD=5.53), until age 18 (23.96, SD= 5.99) and started to decline after age 40 (21.21, SD= 4.99), and 65 until present (21.10, 4.62) (Figure 3). The reliability of the items of CAS was assessed and was found to have a Cronbach's alpha of .89 and .90 for CAS revised. Participants scored in the average range total score of 15.40 (SD=12.29) in physical activities (Table 26 and Figure 4). They scored at 4.83 (SD=4.14) at age 15, 4.10 (SD=3.45) at age 30, 3.63 (SD=3.18) at age 50, and 2.95 (SD=3.29) at 65 and above. In terms of type of exercise, participants scored higher in light exercise (6.91, SD=6.20), followed by moderate (5.69, SD=4.93) and vigorous exercises (2.86, SD=3.92) (See

Table 26 and Figure 5). The PAQ was found to have good reliability, a Cronbach's alpha of 0.89.

The variability in the PAQ was high as seen with high standard deviations (SD).

Participants obtained an occupational prestige of 63.37 (SD=11.57), which indicates this sample was among those with high occupational prestige (See

Table 26). In terms of the category of their occupation, most participants reported that they had managerial occupation (130/150, 88 % of the sample), and few participants had semi-skilled occupation (12%). Concerning their salary, 65 participants reported that they had a salary between $30, 000 to $80,000 a year, 32 had less than $15,000 while 21 had a salary of $16,000 to $30,000 a year (See Table 25). Participants scored high (32.04, SD=5.91) in the measure of their behaviors of spirituality, which had good reliability, a Cronbach's alpha of .80.

Table 26: Predictors of Cognitive Reserve (N=148)

Predictors of CR	M	SD
Full Scale IQ (FSIQ-2 WASI-II raw score)	118.43	16.46
Full Scale IQ (FSIQ-2 WASI-II scale score)	115.89	14.28
Crystalized intelligence (Vocabulary WASI-II raw score)	46.02	5.74
Crystalized intelligence (Vocabulary WASI-II T- score)	64.57	10.30
Fluid intelligence (Matrix Reasoning WASI-II raw score)	16.94	4.93
Fluid intelligence (Matrix Reasoning WASI-II T-score score)	53.83	9.70
Year of education	18.97	4.09
Occupational Prestige Score	63.37	11.57
Newest Vital Sign (NVS)	4.27	1.83
Cognitive Activities at age 6	11.39	3.01
Cognitive Activities at age 6 revised	15.75	4.43
Cognitive Activities at age 12	16.14	4.02
Cognitive Activities at age 12 revised	21.06	5.43
Cognitive Activities at age 18	19.66	4.90
Cognitive Activities at age 18 revised	23.96	5.99
Cognitive Activities at age 40	17.23	3.90
Cognitive Activities at age 40 revised	21.21	4.99
Cognitive Activities at present	17.33	3.83
Cognitive Activities at present revised	21.10	4.62
Cognitive Activities Scale total	80.80	17.73
Cognitive Activities Scale total revised	101.88	23.18
Physical Activity Questionnaire (PAQ) at age 15	4.83	4.14
Physical Activity Questionnaire (PAQ) at age 30	4.10	3.45
Physical Activity Questionnaire (PAQ) at age 50	3.63	3.18
Physical Activity Questionnaire (PAQ) at age 65	2.95	3.29
Physical Activity Questionnaire (PAQ) light total	6.91	6.20
Physical Activity Questionnaire (PAQ) moderate total	5.69	4.93
Physical Activity Questionnaire (PAQ) vigorous total	2.86	3.92
Physical Activity Questionnaire (PAQ) total	15.40	12.29
Spirituality total	32.04	5.91

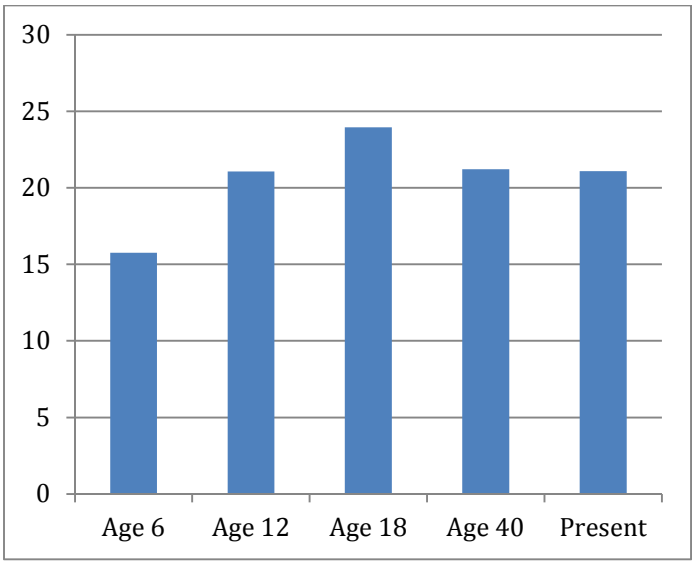


Figure 3: Means of Cognitive Activities

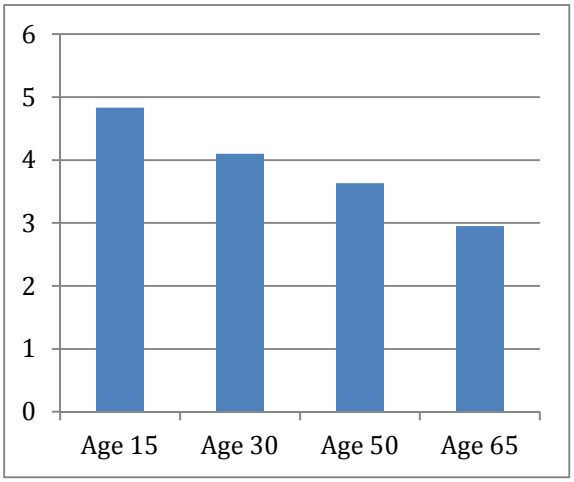


Figure 4: Means of Physical Activities (by Age)

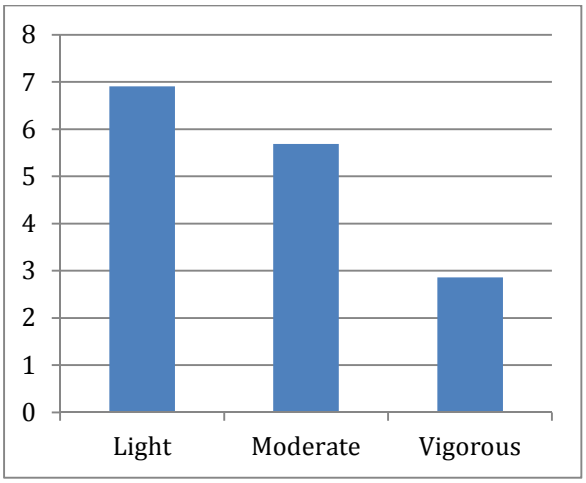


Figure 5: Means of Physical Activities (by intensity)

5.1.5. Cognitive Functions

The means (M) and standard deviations (SD) of various cognitive functions were calculated from their T-scores. The Heaton and colleagues' (Heaton, et al., 1991) performance neuropsychological classifications (Heaton et al., 1991) were used to determine participants' range of cognitive functioning compared to people of the same age. For example, these participants' executive functions (i.e., verbal inhibition and cognitive flexibility) as measured by D-KFES were in the average range compared to their peers (Condition 1: T-score= 51.30, SD=10.13; Conditions 2: T-score=52.55, SD=9.04; Condition 3: T-score= 51.01, SD=11.10; and condition 4: T-score= 52.79, SD=9.69). Participants also obtained an average score in the total D-KFES Design Fluency Test (T-score= 53.68, SD=10.75), which measures executive functions such as fluency in generating visual patterns, creativity in drawing designs, observations of rules, and inhibition of responses. Although the overall average of these three conditions, conditions 1 (52.79, SD=11.21), and condition 2 (53.30, SD=10.10) were average, these participants scored in

the mildly impaired range for condition 3, which assesses inhibition and switching (T-score= 37.73, SD=20.52) (See Table 27).

Pertaining to various aspects of attention, participants performed below average in TMT-B (T-score= 44.03, SD=10.84), which measures visual divided attention. In the WAIS-IV Digit-Span subtest, which evaluates concentration and attention as well as short-term memory and sequencing ability, participants obtained an average score (T-score= 51.28, SD=9.27). In addition, participants of this sample performed in the average range in the WAIS-IV Letter Number Sequencing (T-score= 48.84, SD=7.53) subtest, which assesses concentration and attention (See Table 27).

In the RCFT which assesses visual memory, participants scored in the above average range in immediate visual memory (T-score= 57.13, SD=14.49) and long-term visual memory (T-score= 56.30, SD=14.92) but obtained an average score (T-score =47.65, SD=11.35) in visual recognition. In terms of the recognition variables, participants obtained scores beyond 16th percentile in RCFT copy (Raw-score= 33.92, SD=2.98), time to copy (208.69, SD=89.76 seconds), true positives (9.37, SD=1.90), true negatives (1.75, SD=1.59), and in false negatives (2.69, SD=1.97). Participants in this sample scored in the average range in different auditory verbal memory measured by RAVLT such as immediate auditory verbal memory (T-score= 50.15, SD=12.06), long-term auditory verbal memory (T-score= 53.97, SD=11.83), recall auditory verbal memory (52.80, SD=9.38), and verbal recognition (T-score= 48.58, SD=9.72). There were fewer sematic intrusions (0.56, SD=0.90), phonemic intrusions (0.40, SD=0.69), and intrusions from list B (1.60, SD=2.24) (See Table 27).

Participants had average scores in both tests of verbal fluency FAS (T-score=46.69, SD=10.04) and Animals (T-score= 45.92, SD=12.76). They performed in the below average range (T-score= 41.46, SD=12) in the speed of information processing assessed by TMT-A. They scored in the average range (T-score= 53.97, SD=9.77) in the WAIS-IV Coding subtest, which also measures psychomotor and clerical speed as well as accuracy. Finally, participants performed in the average range (T-score= 51.51, SD=10.51) in a test of visuo-spatial skills (WAIS-IV, Block design). In conclusion, this sample obtained average scores in executive functions, attention, memory (e.g., visual recognition, immediate auditory memory, recall auditory verbal memory, auditory verbal long-term memory, and auditory verbal recognition), verbal fluency, speed of information processing, and visuo-spatial skills. They scored in the above average range in the immediate visual memory and long-term visual memory (See Table 27). This average range score in most of the cognitive functions is also found in the score of the screening measure, MMSE of 28.61 (SD=1.40) (see Table 27). The average score in normative group is 50.

Table 27: Summary of Means and Standard Deviations of Raw Scores and T-scores of Various Tests of Cognitive Functions (N=149)

Cognitive Function	M	SD
Executive Functions		
D-KFES Stroop Conditions 1 Word Raw Score	32.07	7.09
D-KFES Stroop Conditions 1 Word T-Score	51.30	10.13
D-KFES Stroop Conditions 2 Color Raw Score	22.93	4.78
D-KFES Stroop Conditions 2 Color T-Score	52.55	9.04
D-KFES Stroop Conditions 3 Inhibition Raw Score	72.36	26.46
D-KFES Stroop Conditions 3 Inhibition T-Score	51.01	11.10
D-KFES Stroop Conditions 4 Inhibition/Switching Raw Score	75.99	22.34
D-KFES Stroop Conditions 4 Inhibition/Switching T-Score	52.93	9.69

D-KFES Design Fluency Condition 1 Raw Score	8.58	3.13
D-KFES Design Fluency Condition 1 T-Score	52.79	11.21
D-KFES Design Fluency Condition 2 Raw Score	9.66	3.08
D-KFES Design Fluency Condition 2 T-Score	53.30	10.10
D-KFES Design Fluency Condition 3 Raw Score	5.69	3.09
D-KFES Design Fluency Condition 3 T-Score	37.73	20.52
D-KFES Design Fluency Total Raw Score	24.41	8.25
D-KFES Design Fluency Total T-Score	53.68	10.75
Attention		
Trail Making Test B (TMT A) Raw Score	121.37	75.90
Trail Making Test B (TMT A) T-Score	44.03	10.84
WAIS-IV Digit Span Raw Score	25.62	4.93
WAIS-IV Digit Span T-Score	51.28	9.27
WAIS-IV Letter Number Sequencing Raw Score	17.07	3.51
WAIS-IV Letter Number Sequencing T-Score	48.84	7.53
Memory Functions		
Visual Memory		
Immediate Visual Memory (RCFT Immediate Raw Score)	16.59	7.39
Immediate Visual Memory (RCFT Immediate T-Raw)	57.13	14.49
Long Term Visual Memory (RCFT Delayed Raw Score)	16.11	7.41
Long Term Visual Memory (RCFT Delayed T-Score)	56.30	14.92
Visual Recognition (RCFT Recognition Raw Score)	19.69	2.11
Visual Recognition (RCFT Recognition T-Score)	47.65	11.35
Copy RCFT-Raw score	33.92	2.98
Time to Copy	208.69	89.76
Recognition True Positives	9.37	1.90
Recognition False Positives	1.75	1.59
Recognition True Negatives	10.20	1.76
Recognition False Negatives	2.69	1.97
Auditory Verbal Memory		
Immediate Auditory Verbal Memory (RVALT Immediate Raw Score)	5.68	2.06
Immediate Auditory Verbal Memory (RVALT Immediate T-Raw)	50.15	12.06
Long Term Auditory Verbal Memory (RVALT Delayed Raw Score)	9.17	3.47
Long Term Auditory Verbal Memory (RVALT Delayed T-Score)	53.97	11.83

Recall Auditory Verbal Memory (RAVLT Recall raw score)	9.34	3.24
Recall Auditory Verbal Memory (RAVLT Recall T-score)	52.80	9.38
Auditory Verbal Recognition (RVALT Recognition Raw Score)	12.97	1.92
Auditory Verbal Recognition (RVALT Recognition T-Score)	48.58	9.72
Auditory Verbal Raw Score (RAVLT total Raw Score)	45.43	11.51
Auditory Verbal Total Score (RAVLT total T-Score)	56.45	12.31
Total Intrusions from List B	1.60	2.24
Total Semantic Intrusions	0.56	0.90
Total Phonemic Intrusions	0.48	0.69
Language		
FAS Raw Score	39.42	10.99
FAS T-Score	46.69	10.04
Animal Raw Score	18.52	5.60
Animal T-score	45.92	12.76
Speed of Information Processing		
Trail Making Test A (TMT A) Raw Score	46.61	20.10
Trail Making Test A (TMT A) T-Score	41.46	12.00
WAIS-IV Coding Raw Score	55.33	16.18
WASI-IV Coding T-Score	53.97	9.77
Visual Spatial Skills		
WAIS-IV Block Design Raw Score	31.76	10.95
WASI-IV Block Design T-score	51.51	10.51

5.1.6. Bivariate Relationships with Hypertension

Chi-square tests were conducted to identify the associations of risk factors with hypertension in this sample. Participants were put into groups by splitting the sample at the mean or the median. There were significant associations of hypertension with age (i.e., older than 72.5 years); status (i.e., priests and nuns); and family history of hypertension (i.e., those with one of the biological siblings having hypertension). Hypertension was significantly associated with cognitive function (i.e., low cognitive functions); CR (i.e., high cognitive reserve); physical

activities (i.e., high physical activities) and spiritual and religious behaviors (i.e., high spirituality and religious behaviors) (See Table 28).

Although the prevalence of hypertension appeared to be higher among females, white, those with one of the parents with hypertension, PhDs, MDs, and JDs as well as those with managerial occupations, those who slept between 5 to 6 hours at night, and those with many years of education, these associations were not significant (See Table 28).

Table 28: Bivariate Relationship with Hypertension[2]

	Normotensive		Hypertensive		Total	
Characteristics	N	%	N	%	N	$\chi^2(1)$
Age Group						26.194***
<72.5	42	61	27	39	69	
>=72.5	15	20	62	81	77	
Total	57	39	89	61	146	
Gender						2.64
Male	36	45	44	55	80	
Female	21	32	45	68	66	
Total	57	39	89	61	146	
Status						19.116***
Consecrated	18	23	61	77	79	
Lay	39	58	28	42	67	
Total	57	39	89	61	146	
Years of education						0.746
Less than or equal to 18.1	35	42	49	58	84	
More than 18.1	20	35	38	66	58	
Total	55	39	87	61	142	
Category of occupation						0.673
Managerial	50	39	77	61	127	
Semi-skilled	7	41	10	59	17	

[2] * p <.05, **p<.01, *p<.001

Total	57	39	88	61	145	
Hours of sleep						4.58
0 to 4	1	50	1	50	2	
5 to 6	14	31	31	69	45	
7 to 8	39	46	46	54	85	
More than 8	3	25	9	75	12	
Total	57	39	88	61	145	
Parent with hypertension						6.551
No	17	49	18	51	35	
Yes	22	29	53	71	75	
NS	4	50	4	50	8	
N/A	14	52	13	48	27	
Total	57	39	88	61	145	
Sibling with hypertension						14.08**
No	27	51	26	49	53	
Yes	11	20	44	80	55	
NS	5	46	6	55	11	
N/A	14	54	12	46	26	
Total	57	39	88	61	145	
Spirituality						20.763***
Low spirituality	41	59	28	41	57	
High spirituality	16	22	57	78	85	
Total	57	40	85	60	142	
Cognitive functions						9.927**
Low cognitive functions	19	26	54	74	73	
High cognitive functions	38	51	36	49	74	
Total	57	39	90	61	147	
Cognitive activities scale						0.032
Low cognitive activities	31	40	46	60	77	
High cognitive activities	26	39	41	61	67	
Total	57	40	87	60	144	
Physical activities questionnaire						6.938**
Low physical activities	38	49	39	51	77	
High physical activities	19	28	49	72	68	
Total	57	39	88	61	145	
Cognitive reserve						12.175***
Low cognitive reserve	39	53	35	47	74	
High cognitive reserve	18	25	55	75	73	

Total	57	39	90	61	147

5.1.7. Controlled Versus Uncontrolled Hypertension

There were significant associations of controlled hypertension with age (i.e., older than 72.5 years); status (i.e., priests and nuns); duration of hypertension (i.e., those with 10 years or less of duration of hypertension); and family history of hypertension (i.e., those having one parent with hypertension). Controlled hypertension was significantly associated with cognitive functions (i.e., high cognitive functions); CR (i.e., high cognitive reserve); physical activities (i.e., high physical activities); and spiritual and religious behaviors (i.e., high spiritual and religious behaviors) (See Table 29).

Although the prevalence of controlled hypertension appeared to be higher among males, whites, those with a sibling with hypertension; PhDs, MDs, and JDs as well as those with managerial occupations; salaries between $30, 001 to $80,000; who slept between 7 to 8 hours at night; those with many years of education, these associations were not statistically significant (See

Table 29).

In terms of hypertensive drugs, controlled hypertension was significant associated with Diuretics; ACEIs, ARBs, CCBs, BBs, Vasodilators, combined two antihypertensive drugs, combined three antihypertensive drugs (See Table 29).

Table 29: Controlled Versus Controlled Hypertension[3]

	Uncontrolled		Controlled		Total	
Characteristics	N	%	N	%	n	$\chi^2(1)$
Age Group						26.794***
<72.5	9	41	16	24	55	
>=72.5	13	59	51	76	74	
Total	22	100	67	100	129	
Gender						2.017
Male	11	50	35	52	72	
Female	11	50	32	48	57	
Total	22	100	67	100	129	
Status						16.561***
Consecrated	11	50	51	76	77	
Lay	11	50	16	24	52	
Total	22	100	67	100	129	
Years of education						3.301
Less than or equal to 18.1	16	73	34	52	74	
More than 18.1	6	27	32	49	53	
Total	22	100	66	100	127	
Category of occupation						5.841
Managerial	18	82	60	91	112	
Semi-skilled	3	14	6	9	15	
Total	22	100	66	100	128	
Hours of sleep						5.954
0 to 4	1	5	0	0	2	
5 to 6	7	32	21	32	39	
7 to 8	11	50	40	61	78	
More than 8	3	14	5	8	9	
Total	22	100	66	100	128	
Duration						51.388***
10 years or less	2	15	16	49	21	

[3] *p<.05, **p<.01, *p<.001

More than 10 years	7	54	14	42	21	
Total	13	100	33	100	80	
Parent with hypertension						17.661**
No	3	14	14	21	30	
Yes	15	68	39	59	66	
NS	3	14	1	2	7	
N/A	1	5	12	18	25	
Total	22	100	66	100	128	
Sibling with hypertension						12.377
No	9	41	23	35	49	
Yes	10	46	29	44	46	
NS	2	9	3	5	9	
N/A	1	5	11	17	24	
Total	22	100	66	100	128	
Spirituality						17.462***
Low spirituality	11	52	17	27	55	
High spirituality	10	48	47	73	70	
Total	21	100	64	100	125	
Cognitive functions						21.013***
Low cognitive functions	6	27	46	68	63	
High cognitive functions	16	73	22	32	67	
Total	22	100	68	100	130	
Cognitive activities scale						0.124
Low cognitive activities	12	55	34	52	66	
High cognitive activities	10	46	31	48	61	
Total	22	100	65	100	127	
Physical activities questionnaire						6.296*
Low physical activities	11	50	28	42	66	
High physical activities	11	50	38	58	62	
Total	22	100	66	100	128	
Cognitive reserve						8.948*
Low cognitive reserve	10	46	24	35	60	
High cognitive reserve	12	55	44	65	70	
Total	22	100	68	100	130	
Hypertensive medication						
Diuretics	2	9	22	34	25	17.278***
Angiotensin converting enzyme (ACEIs)	5	23	26	40	31	21.513***

Angiotensin Receptor Blockers (ARBs)	5	23	11	17	17	6.446*
Renin inhibitors	0	0	0	0	0	
Calcium channel blockers (CCBs)	3	14	18	28	21	13.921**
Beta blockers (BBs)	7	32	34	52	41	30.994***
Vasodilators	1	5	12	18	14	7.570*
Combined two drugs	8	36	21	32	29	17.432***
Combined three drugs	0	0	13	20	13	13.814**
N/A	7	32	4	6	48	78.930***
Combined four or more drugs	0	0	5	8	5	4.965

5.2. Hypothesis Tests

5.2.1. Data Analysis

The Statistical Package for Social Science (SPSS), version 17.0 (2009) and AMOS were used for data analyses. In all analyses, raw scores were used as it is typical in the cognitive reserve literature. For descriptive purposes, scale scores were also calculated. Pre-analysis data screening was performed prior to actual multivariate analyses to test statistical assumptions, evaluate outliers and missing data (Mertler & Vannatta, 2010). Pre-screening of data consisted of exploring the missing data, outliers, normality, linearity, and homoscedasticity (i.e., the assumption that variability in scores for one continuous variable is the same at all values of another continuous variable). As per Mertler and Vannatta's suggestions (2010), for multivariate analyses, missing values were imputed using mean substitution. A sample of 150 participants was used for multivariate analyses. However, some values were missing which resulted in 148 or 147 participants.

In testing the three assumptions (e.g., normality, linearity, and homoscedaticity), univariate normality was assessed using the statistical values of skewness (i.e., quantitative

measure of the degree of symmetry of a distribution to the mean), kurtosis (quantitative measure of the degree of peakness of distribution to the mean) or Kolmogoro-Smirnov statistics (i,e., finding whether the sample is normally distributed). Linearity was determined by using the residual plots or prediction errors (i.e., portions of score not accounted for in multivariate analysis) and by inspecting bivariate scatterplots (i.e., looking for the elliptical shape of scatterplot) (Mertler & Vannatta, 2010). In univariate analysis, homogeneity of variance was assessed with Levene's test (i.e., test whether the samples come from populations with the same variances) (Mertler & Vannatta, 2010, p.33). In multivariate analysis, homoscedasticity and heteroscedaticity (i.e, the violation of homoscedasticity) were determined using the Box's M test for equality of variance-covariance matrices. This test allowed the evaluation of the null hypothesis that the covariance matrices are equal (Mertler & Vannatta, 2010).

In performing a MANOVA, this study examined first the F ratio and the p value for Box's test. Whenever the p value was significant at $p < .001$ with extremely unequal group sample sizes, Pillai's Trace test was used as the statistical method. However, whenever the p value is not significant at $p < .001$ with fairly equal group sample sizes, Wilks' Lambda test was used as the statistical method. After this procedure, the investigator interpreted the main effect for each independent variable (IV) on the combined dependent variable (DV). Whenever the factor interaction in the MANOVA was significant, univariate ANOVA was conducted (Mertler & Vannatta, 2010).

Exploratory Factor Analysis (EFA), one of the most commonly used types of Factor Analysis (FA), was conducted in this study in order to cluster the predictors. In conducting factor analysis, the Data Reduction Statistical Test was used to analyze the data. To determine the

appropriate number of components to retain, this study extracted the eigenvalue (i.e., amount of total variance explained in each factor), variance, scree plot (i.e., the graph of the magnitude of each eigenvalue plotted against their ordinal numbers) and residual (Mertler & Vannatta, 2010). As suggested by Mertler and Vannatta (2010), the following components were retained: (1) eigenvalue greater than 1; (2) variance that accounts for at least 70% of total variability; (3) those factors in the scree plot within the sharp descent, before eigenvalues level off; and (4) residuals generated by the model if only a few residuals exceed .05. In case several reproduced correlations differ, this study included more components. Other factor analysis was conducted if more components need to be retained.

5.2.2. Hypothesis One

A maximum likelihood Confirmatory Factor Analysis (CFA) was conducted to determine whether the 25 cognitive function indicators (i.e., the total score of the four conditions of the Stroop Color Word Interference Test and of the Design Fluency Test); attention (i.e., raw score of TMT-B, Digit Span and Letter Number Sequencing); memory (i.e., the score of immediate memory, long-term memory, and recognition of the RAVLT and the RCFT); language (i.e., score of Vocabulary of the WASI II, total score of FAS and Animals); Speed of Information Processing (i.e., score of the TMT-A and Coding subtest of the WAIS-IV); and Visuo-spatial skills (i.e., the score of copy RCFT and Block Design of the WAIS-IV) clustered together to measure the same construct, that is, cognitive function (Hypothesis One, Figure 6). To ensure that results were robust and generalizable, a bootstrap analysis involving 200 bootstrap samples were generated in order to provide stability of parameter estimates. The regression weights (i.e., factor loadings) were found to be all statistically significant, and their bias-corrected confidence

intervals did not contain the value zero and all the loading factors were found reliable. A close look at to the model fit indices, however, indicated that the model fitted the data poorly because they all fell outside of acceptable ranges. The chi-square was significant, the value of chi-square/df ratio was above 3 (i.e., 1034.92/275= 3.79), the Goodness of Fit Index (GFI= .63), Comparative Fit Index (CFI= .68), Normed Fit Index (NFI= .62), Relative Fit Index (RFI= .58 and Incremental Fit Index (IFI = .69) all fell below .90 and the RMSEA was found to be above .08.

Therefore, there was a need to improve the model fit by examining modification indices (MI) in the analysis to find out the part of the model which needed respecification. Elevated MI (i.e., values in excess of 30) were inspected and used as the basis for making model modification. Using this approach, it was discovered that high MI values were obtained for nine pairs of error variances (e1-e2, e11-e13, e11-e12, e22-e23, e18-e19, e15-e13, e14-e13, e14-e11, and e14-e15) indicating that if these error terms were permitted to correlate that it would improve model fit. Since these pairs of error terms were associated with scores from variables that came from the same test or from tests assessing highly similar constructs, it was deemed justifable to change the model to allow these error terms to be correlated.

Based on this, a second CFA was completed where all 25 variables were still assumed to contribute to a one-factor cognitive function construct but the relevant error terms were allowed to co-vary. The results of the one factor model with correlated errors showed that all the factor loadings were significant as well as all the nine-error co-variances (i.e., correlations between the nine pairs of error terms). In addition, bootstrap analysis confidence intervals were found reliable and the model fit statistics were considerably improved. Although the chi-square was still

significant, the chi-square/df ratio (463.25/266= 1.74) fell below 3.0 and CFI (.92), TLI (.91), and IFI (.92) were all above .90 while the RMSEA was below .08. However, GFI (.81), NFI (.81), and RFI (.81) were found to be below .90. Although these variations suggested that some aspects of model fit were still inadequate, the inspection of resulting MIs revealed none that justified any further model re-specification. Based upon these two CFAs, it was concluded that there was sufficient evidence supporting the one-factor model of cognitive functions (Tables 30 and 31).

For further analysis, a cognitive factor score was estimated for each participant using Principal Component Analysis (PCA) with orthogonal rotation, forcing the number of factor to one.

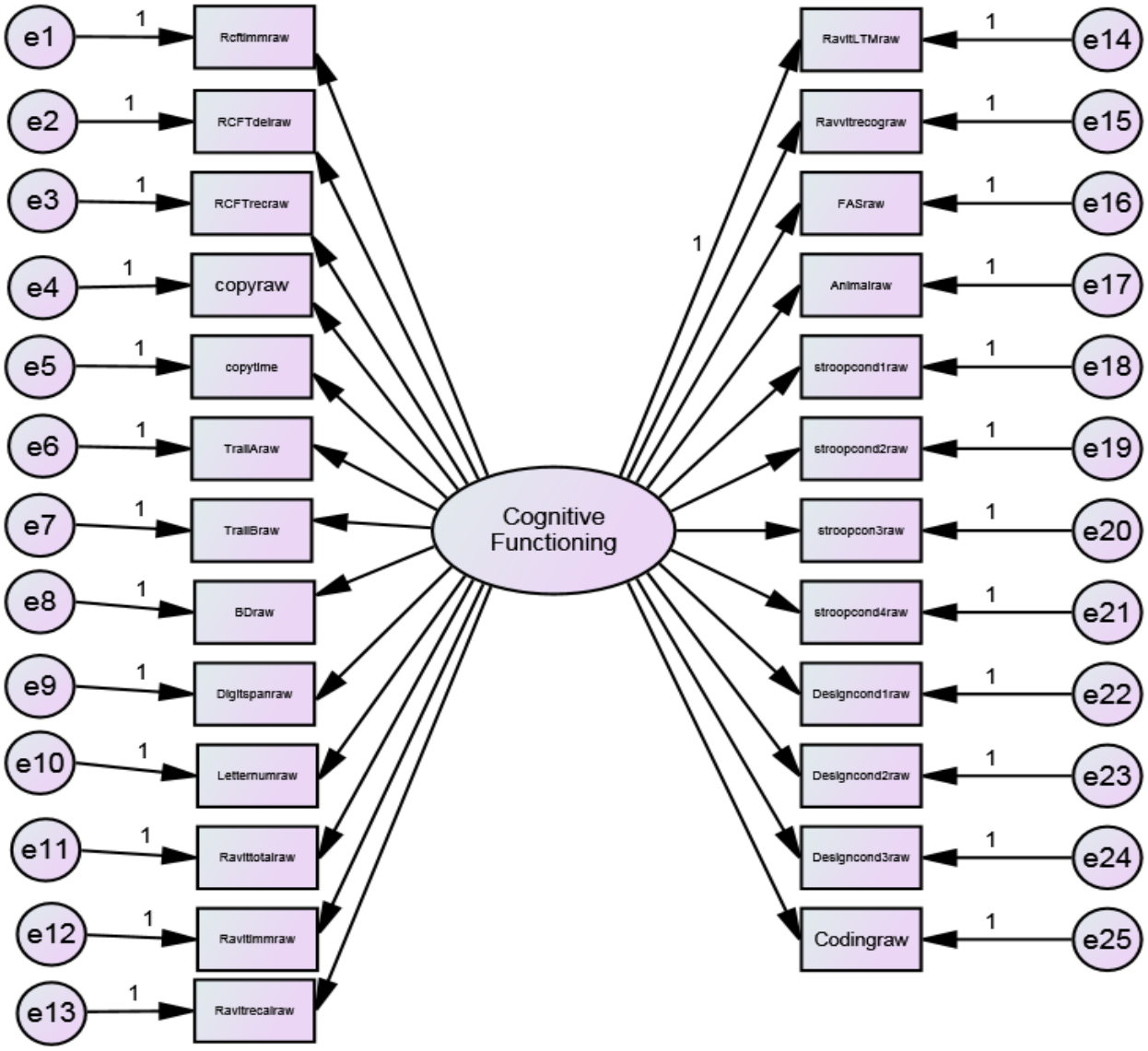


Figure 6: Confirmatory Factor Analysis: One factor model of cognitive function

Table 30: Standardized Regression Weights of CFA of the Original and Revised models of Cognitive Functions.[4]

Cognitive function	Original one factor model of cognitive functions	Revised one factor model 2
Long Term Auditory Verbal Memory (RVALT Delayed Raw Score)	0.69	0.64
Auditory Verbal Recognition (RVALT Recognition Raw Score)	0.56	0.51
FAS Raw Score	0.51	0.50
Animal Raw Score	0.66	0.66
D-KFES Stroop Conditions 1 Word Raw Score	-0.62	-0.62
D-KFES Stroop Conditions 2 Color Raw Score	-0.43	-0.42
D-KFES Stroop Conditions 3 Inhibition Raw Score	-0.75	-0.77
D-KFES Stroop Conditions 4 Inhibition/Switching Raw Score	-0.74	-0.76
D-KFES Design Fluency Condition 1 Raw Score	0.58	0.58
D-KFES Design Fluency Condition 2 Raw Score	0.68	0.69
D-KFES Design Fluency Condition 3 Raw Score	0.72	0.73
WAIS-IV Coding Raw Score	0.85	0.86
Immediate Visual Memory (RCFT Immediate Raw Score)	0.73	0.69
Long Term Visual Memory (RCFT Delayed Raw Score)	0.72	0.67
Visual Recognition (RCFT Recognition Raw Score)	0.36	0.33
Copy RCFT-Raw score	0.54	0.54
Time to Copy	-0.49	-0.50
Trail Making Test A (TMT A) Raw Score	-0.69	-0.71
Trail Making Test B (TMT B) Raw Score	-0.85	-0.87
WAIS-IV Block Design Raw Score	0.63	0.64
WAIS-IV Digit Span Raw Score	0.58	0.59
WAIS-IV Letter Number Sequencing Raw Score	0.60	0.61
Auditory Verbal Raw Score (RAVLT total Raw Score)	0.72	0.69
Immediate Auditory Verbal Memory (RVALT Immediate Raw Score)	0.50	0.46
Recall Auditory Verbal Memory (RAVLT Recall raw score)	0.68	0.63

Table 30 continues.

e1<-->e2

[4] All the regression weights were found to be significant at p< .05 or lower.

0.88
e11<-->e13
0.48
e11<-->e12
0.47
e22<-->e23
0.55
e18<-->e19
0.45
e15<-->e13
0.30
e14<-->e13
0.71
e14<-->e11
0.52
e14<-->e15
0.25

Table 31: Summary of Model Fit Indices for two Models of Cognitive Functions.

Statistic Fit	Original one factor model of cognitive functions	Revised one factor model
CMIN	1034.95	463.25
DF	275.00	266.00
CMIN/DF	3.76	1.74
GFI	0.63	0.81
AGFI	0.56	0.76
NFI	0.62	0.83
RFI	0.58	0.81
IFI	0.69	0.92
TLI	0.66	0.91
CFI	0.68	0.92
RMSEA	0.14	0.07

5.2.3. Hypothesis Two

One-way between participants Multivariate Analyses of Variance (MANOVA) was conducted to determine the significance of the difference in the means of cognitive functions between normotensive and hypertensive participants (Hypothesis Two). The cognitive functions

measure that will be included in this analysis are executive functions (i.e., the total score of the four conditions of the Stroop Color Word Interference Test and of the Design Fluency Test); attention (i.e., the raw score of TMT-B, Digit Span and Letter Number Sequencing); memory (i.e., the score of immediate memory, long-term memory, and recognition of RAVLT and RCFT); language (i.e., total score for FAS and Animals); Speed of Information Processing (i.e., the score of the TMT-A and of Coding subtest of the WAIS-IV); and Visuo-spatial skills (i.e., the score of copy and Time to copy of RCFT and of Block Design of the WAIS-IV). Hypertension was measured either as a dichotomous variable (i.e., hypertension or normotensive) and a continuous variable, which is the average of three consecutive readings of blood pressure taken three consecutive days. Prior to the test, bivariate correlations were conducted to find out the correlations between variables. MANOVA results revealed a nonsignificant trend between the normotensive and hypertensive participants, Wilks'$\wedge$ = .767, F (23,12) = 1.56, p = .06. Nevertheless, Analysis of variance (ANOVA) was conducted on each dependent variable as a follow up test to MANOVA. Difference in the means between normotensive and hypertensive participants were significant for executive functions measured by Stroop condition 4 (i.e., verbal inhibition/switching), Design Fluency condition 1, $F(1,135) = 4.90$, p= .029; condition 2, $F(1, 135) = 9.41$, p= .003; and condition 3 (i.e., visual inhibition/switching), $F(1,135) = 4.78$, p= .030; attention measured by TMT-B (i.e. divided attention), $F(1, 135) = 15.75$, p< .0001 and Letter Number Sequencing (i.e., concentration and attention), $F(1,135) = 6.77$, p= .010; immediate visual memory, $F(1, 135) = 9.05$, p= .003; recall visual memory, $F(1,135) = 8.27$, p= .005; recall auditory verbal memory, $F(1, 135) = 6.24$, p= .014; auditory verbal recognition, $F(1, 135) = 8.03$, p= .005; verbal fluency measured by Animal

fluency Test, $F(1,135) = 9.00$, p= .003; speed of information processing measured by Coding, $F(1, 135) = 20.06$, p= .000 and TMT-A, $F(1, 135) = 9.73$, p= .002; and visuo-spatial skills (Block Design WAIS-IV), $F(1, 135) = 4.70$, p= .032. Differences in means between normotensive and hypertensive participants were not significant for executive functions measured by Stroop condition 1, $F(1,14) = 2.92$, p= .090, condition 2, *F* $F(1, 135) = .34$, p= .055, and condition 3, $F(1, 135) = 2.57$, p= .112, attention measured by Digit Span WAIS-IV, $F(1,135) = 2.74$, p= .100, visual recall memory, $F(1,135) = 3.40$, p= .067; immediate auditory verbal memory, $F(1,135) = 2.65$, p= .106, long-term auditory verbal memory, $F(1,135) = 3.68$, p= .057, and verbal fluency measured by FAS, $F(1,135) = .68$, p= .413. Table 32 presents means and standard deviations of cognitive functions between normotensive and hypertensive participants.

Table 32: Means and Standard Deviations of Cognitive Functions Between Normotensive and Hypertensive Participants[5]

	Normotensive		Hypertens
Mean Scores and Standard Deviations for Measures of Cognitive Functions	M	SD	M
Executive Functions			
D-KFES Stroop Conditions 1 Word Raw Score	30.75	6.51	32.84
D-KFES Stroop Conditions 2 Color Raw Score	22.58	3.84	23.07
D-KFES Stroop Conditions 3 Inhibition Raw Score*	68.11	21.22	75.46
D-KFES Stroop Conditions 4 Inhibition/Switching Raw Score*	69.38	16.93	80.21
D-KFES Design Fluency Condition 1 Raw Score*	9.29	2.64	8.11
D-KFES Design Fluency Condition 2 Raw Score**	10.64	2.68	9.07
D-KFES Design Fluency Condition 3 Raw Score*	6.44	2.88	5.29
Attention			
Trail Making Test B (TMT B) Raw Score*	91.16	54.57	141.28
WAIS-IV Digit Span Raw Score	26.44	4.49	25.02
WAIS-IV Letter Number Sequencing Raw Score*	18.02	3.61	16.45
Memory Functions			
Visual spatial Memory			
Immediate Visual Memory (RCFT Immediate Raw Score)**	18.83	5.86	15.21
Long Term Visual Memory (RCFT Delayed Raw Score) *	18.46	6.58	14.92
Visual Recognition (RCFT Recognition Raw Score)	20.13	1.82	19.48
Auditory Verbal Memory			
Immediate Auditory Verbal Memory (RVALT Immediate Raw Score)	6.04	2.11	5.47
Long Term Auditory Verbal Memory (RVALT Delayed Raw Score)*	9.89	2.96	8.80
Recall Auditory Verbal Memory (RAVLT Recall raw score)**	10.22	2.48	8.92
Auditory Verbal Recognition (RVALT Recognition Raw Score)	13.55	1.39	12.64
Auditory Verbal Raw Score (RAVLT total Raw Score)	48.69	10.28	43.55
Language			
FAS Raw Score	40.29	10.62	38.77
Animal Raw Score**	20.11	5.66	17.30
Speed of Information Processing			

[5] Univariate ANOVAs, *= $p < .05$; ** = $p < .01$

Trail Making Test A (TMT A) Raw Score **	40.18	18.94	50.77
WAIS-IV Coding Raw Score**	62.49	14.62	50.67
Visual Spatial Skills			
WAIS-IV Block Design Raw Score*	34.25	11.29	30.20

One-way between Participants Analysis of Variance (ANOVA) was conducted to evaluate the significant mean difference in cognitive functions using the PCA factor among the normotensive and hypertensive participants. There was a significant mean difference in cognitive functions among normotensive and hypertensive participants, $F(1,135) = 15.78$, $p < .0001$.

Figure 7 presents means and standard deviations of cognitive functions between normotensive and hypertensive participants.

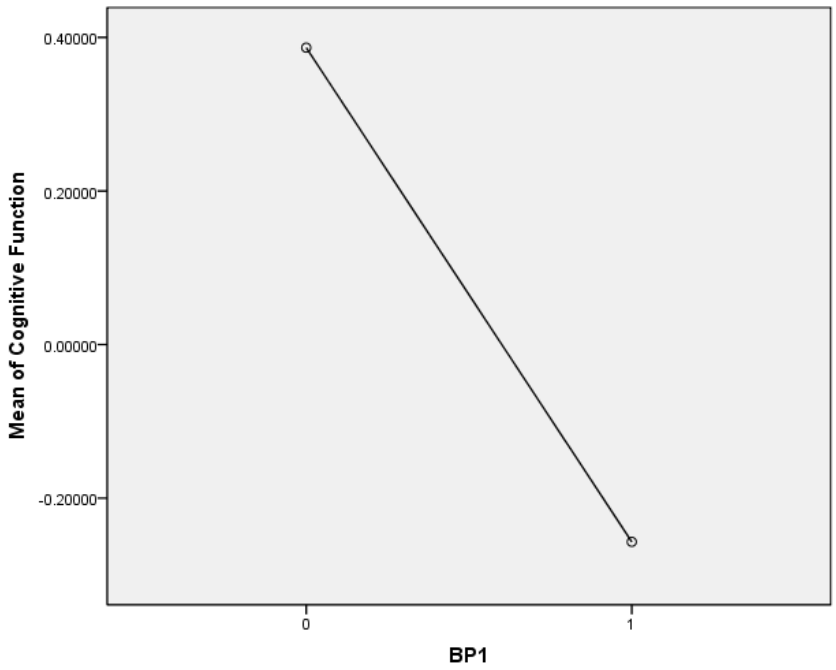


Figure 7: Means and Standard Deviations of Cognitive Functions Between Normotensive and Hypertensive Participants

5.2.4. Hypothesis Three

One-way between Participants Multivariate Analysis of Covariance (MANCOVA) was performed to evaluate whether there were statistically significant mean differences in cognitive functions among hypertensive and normotensive participants after adjusting for age, gender, number of medications, medical conditions, and metabolic syndrome (i.e., presence of DM and hyperlipidemia). The cognitive functions measure that were included in this analysis were executive functions (i.e., the total score of the four conditions of the Stroop Color Word Interference Test and of the Design Fluency Test); attention (i.e., the raw score of the TMT-B, Digit Span and Letter Number Sequencing); memory (i.e., the score of immediate memory, long-term memory, and recognition of the RAVLT and the RCFT); language (i.e., score of Vocabulary of the WASI II, total score for FAS and Animals); Speed of Information Processing (i.e., the score of TMT-A and Coding subtest of the WAIS-IV); and Visuospatial skills (i.e., the score of copy RCFT and Block Design of the WAIS-IV).

MANCOVA was not conducted because the MANOVA in hypothesis 2 was not significant. Therefore, an One-way between Participants Analysis of Covariance (ANCOVA) was performed to evaluate the statistically significant mean differences in the cognitive function factor score between normotensive and hypertensive participants after adjusting for age, gender, number of medications, and number of medical conditions as well as the presence of diabetes mellitus, obesity, hypercholesterimia, hyperlipidemia, depression, Vitamin B12 and iron deficiency/anemia, and stroke/ischemia event. Prior to this analysis, bivariate correlations were conducted to find out the correlations between the cognitive function factors and various covariates. Significant correlations were only found between cognitive function factor with age (-.698, $p < .0001$), number of medical diagnoses (-.232, $p = .005$), and number of medications (-

.380, p< .0001). There was a significant interaction between age and blood pressure group (BP). Therefore, only these significant variables were included in further analyses. Before conducting the ANCOVA, assumptions were tested, unfortunately regression slopes were heterogeneous between BP groups for the relationship of age and cognitive function. The interaction term BP* age was a significant predictor of cognitive function score. Therefore, a general linear regression was conducted instead of ANCOVA. In this analysis, there were significant differences in means in cognitive functions between normotensive and hypertensive participants after controlling for the blood pressure and age interaction, $F(7,136)= 6.27$, $p=.013$ and age, $F(7,136)= 72.05$, $p<.0001$. However, there were no significant differences in means in cognitive functions between normotensive and hypertensive participants after controlling for number of medical conditions, $F(7,136) = .02$, $p= .894$ and number of medications, $F(7,136)= .98$, $p= .325$. The complete model accounted for 51% of the variance in cognitive decline while age accounted for 34.2% ($R^2= .34$), hypertension for 4% ($R^2= .04$), number of medications for 1% ($R^2= .01$), and number of medical diagnosis for 0.2% (.002). Therefore, number of medications and medications diagnoses were not used as predictors in the final regression model. We conducted another analysis using age and the interaction between blood pressure and age as predictors. There was a significant difference in cognitive functions between normotensive and hypertensive participants after controlling for age and the interaction between blood pressure and age, $F(3, 142)= 47.33$, $p<.0001$. The full model (i.e., age, hypertension, and interaction BP x age) accounted for 50% ($R^2= .497$) of the variance in cognitive function with age accounting for 41.1% ($R^2= .41$) and hypertension accounting for 3% ($R^2= .028$).

Table 33 shows the effect of age and hypertension on cognitive functions between normotensive and hypertensive participants after controlling for age. Figure 6 shows the interaction effect graphically. The difference between normotensive and hypertensive groups is large in older people.

Table 33. Mean Cognitive Function Factor Score for Age and BP Groups

BP1	Age	Mean	N	SD
Normotensive	.00 <72.5	0.64	42	0.52
	1.00 >72.5	-0.34	15	0.86
	Total	0.38	57	0.76
Hypertensive	.00 <72.5	0.56	27	0.65
	1.00 >72.5	-0.60	63	1.01
	Total	-0.25	90	1.06
Total	.00 <72.5	0.61	69	0.57
	1.00 >72.5	-0.55	78	0.98
	Total	-0.01	147	1.00

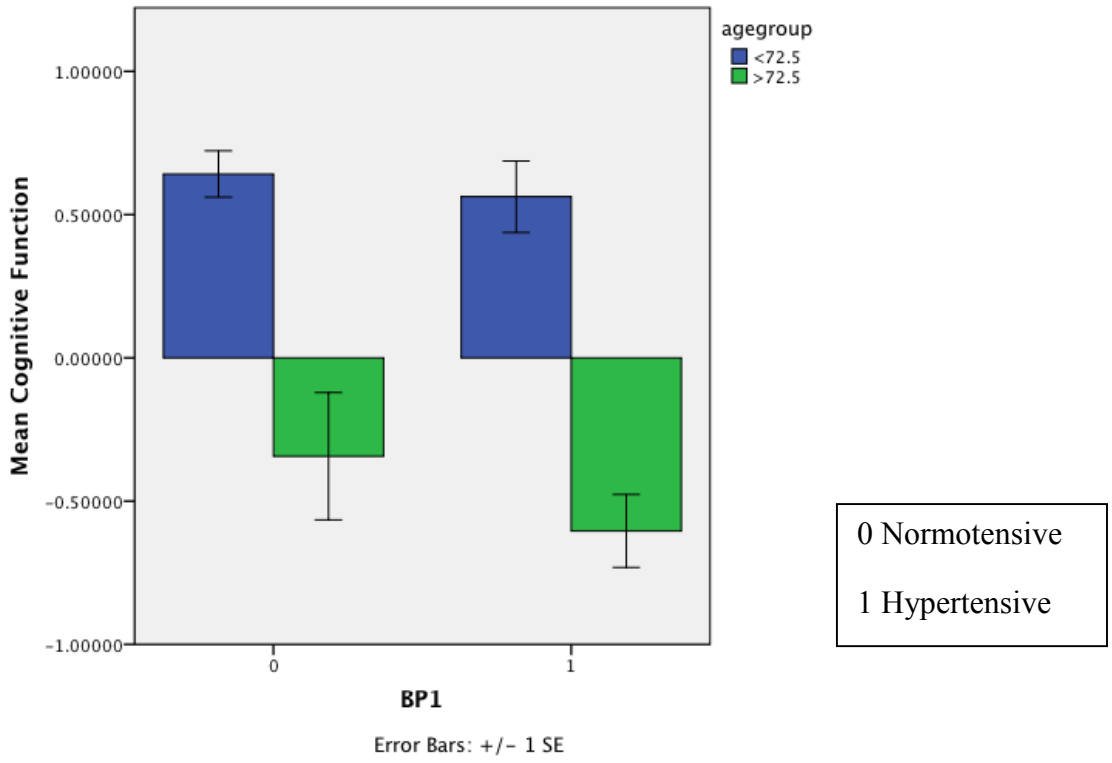


Figure 8: Interaction Effect of BP and Age on Cognitive Functions

5.2.5. Hypothesis Four

A Confirmatory Factor Analysis (CFA) was conducted to determine whether proxies of cognitive reserve cluster together to measure the same construct, that is, cognitive reserve (Hypothesis Four). The cognitive reserve measures that were included were premorbid socioeconomic status (i.e., Family SES level), premorbid intelligence (i.e., the raw score of the FSIQ-2 of the WASI-II), education (i.e., the years of education and the score of health literacy), premorbid leisure activities (i.e., the total score for the CAS revised and the self-report questionnaire on spirituality and religiousness), occupational attainment (i.e., the Prestige score), and physical activities (i.e., frequency of moderate exercise during midlife).

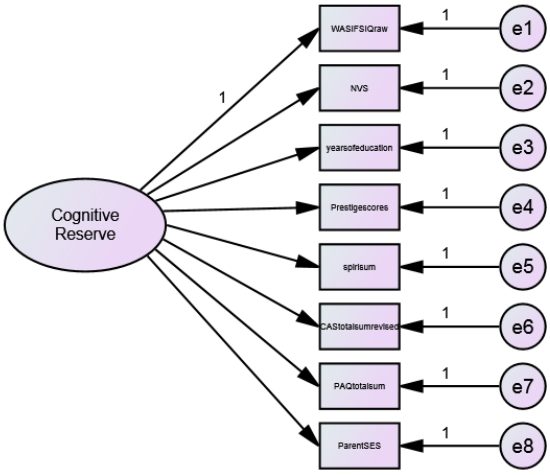


Figure 9: One Factor Model of Cognitive Reserve

The results of the CFA revealed five significant regression weights (i.e., WASIFSIQ, years of education, occupational prestige, Spirituality and Religious behaviors, and Physical Activity Questionnaire) and three non-significant loading factors (i.e., NVS, CAS revised, and Parent SES). In addition, overall model fit was poor because the chi-square ratio/df was above 3 and other fit indices (i.e., NFI, RFI, CFI, IFI, and TLI) were below .8 except GFI (See Table 36). The model was re-specified where the three variables which produced non-significant loadings were removed. The examination of the results of the revised model shows that all five variables loaded significantly on the single cognitive reserve factor (see Table 36). However, model fit statistics are generally very poor because all other fit statistics were below .90 except the GFI (See Table 36). These results indicated that the model still presented some problems with misfit. Examination of MIs did not reveal anything supporting the change of any parameters except one, that is, allowing the error terms for spirituality scores and PAQ scores to correlate. It could be argued that this correlation between the two variables share unintended variance because they are

both measures relating to behavioral activity. By permitting the error terms to correlate, this unintended source of covariability can be taken into account when assessing model fit.

Based on these results another revised model was run in which the errors for spirituality scores and PAQ scores were permitted to correlate. The results of this re-revised model revealed satisfactory values of most model fit statistics with a non- significant chi-square. In this new model, PAQ score was not significantly correlated with Spirituality score (See Table 36). However, when the error terms for PAQ scores and Spirituality scores were permitted to correlate, the previously significant regression weight for PAQ scores was no longer found. Another revised model was conducted where PAQ score was removed. The following diagram shown in Figure 10 represents this new model. The results of this model indicated a stronger model where all the factor loadings were significant and all model fit statistics fell above .90 except for RFI (See Table 36). This new model of cognitive reserve construct was represented by four observed variables (i.e., WASIFSIQ, years of education, prestige scores, and spirituality scores) (See Figure 10).

Figure 10 shows the revised model of CFA presented in the following diagram (See Figure 10).

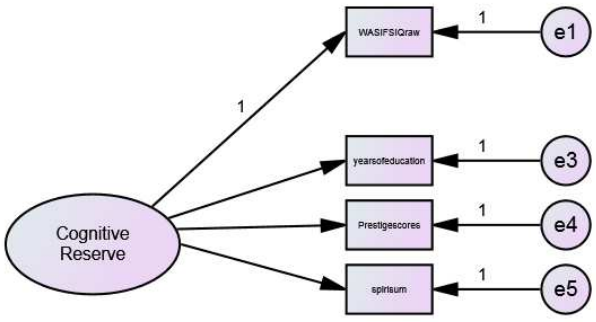


Figure 10: Revised One Factor Model of Cognitive Reserve

Finally, the fifth CFA was conducted utilizing the EFA with Principal Axis Factor as extraction model for one factor preset without any rotation possible. Factor analysis was conducted previously to determine what, if any, underlying structure exists for measures of the following eight CR variables. EFA was conducted utilizing a varimax rotation. Four criteria were used to determine the appropriate number of components to retain: eigenvalue, variance, scree plot, and residuals. Criteria indicated that three components were extracted and retained. After rotation, the first component accounted for 24.12 % of the variance, the second for 21.12% of variance, and the third for 18.11%. Component 1 included positive variables WASIFSIQ, years of education and occupational prestige. This component was named cognitive assets. Component 2 was comprised of two positive items (i.e., Physical activities scores (PAQ) and Spirituality Scores) and one negative item (i.e., Health literature scores, NVS). This component was designated as non-cognitive activity. Component 3 included positive items NVS, CAS, and Parent SES and was named cognitive activity (See Table 34: Component Loadings). The Figure 11 shows the diagram of these three components of the CR (See Figure 11).

Table 34: Component Loadings

	Loading
Component 1: Cognitive Assets	
WASIFSIQ	0.73
Years of education	0.83
Prestige	0.74
Component 2: Noncognitive Activities	
Spirituality score	0.71
PAQ score	0.81
NVS	-0.53
Component 3: Cognitive Activities	
Parent SES	0.58

CAS	0.81
NVS	0.61

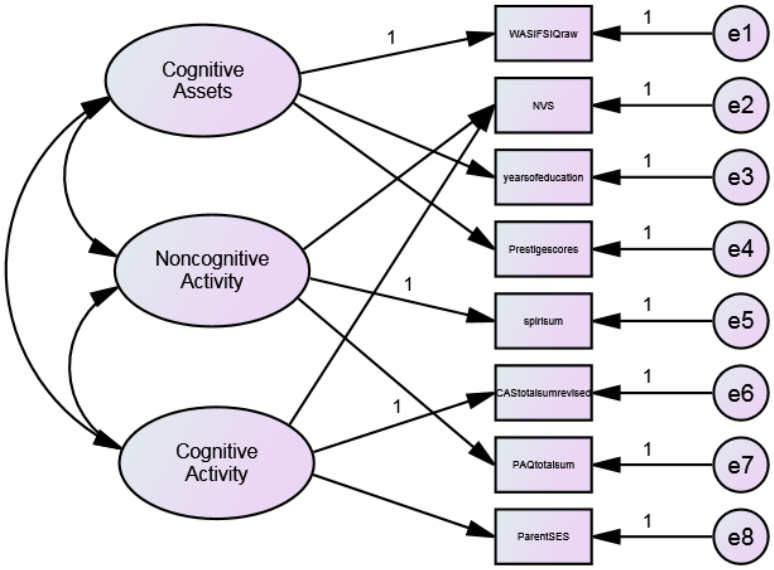


Figure 11: Correlated Three-Factor Model Based on EFA Results

The last CFA conducted with these correlated three-factor model indicated that some of the model fit indices are satisfactory and that all regression weights except that for NVS was significant (See Table 35). Therefore, another CFA was conducted without NVS and the model was found to be inadmissible because there was a negative variance estimate for e5. Therefore, the construct of CR in this study was treated as a single factor measured using the four significantly loading variables (i.e., WASI FSIQ, Years of education, Prestige scores, and spirituality) (See Figure 10).

Table 35: Standardized Regression Weights of the Original and Revised Models of CR*[6].

CR Factors	One factor model of CR	5 loading factors for CR.	One correlated error	4 loading factors for CR	3 factor models of CR.
WASIFSIQraw	0.58*	0.55*	0.58*	0.58*	0.63*
NVS	0.04	---	---	---	-0.28
Years of education	0.67*	0.64*	0.70*	0.69*	0.71*
Prestige score	0.70*	0.73*	0.68*	0.69*	0.63*
Spirituality summary	0.42*	0.44*	0.39*	0.39*	0.82*
PAQ total	0.20*	0.23*	0.13	---	0.48*
CAS total	0.16	---	---	---	0.32*
Parent SES	0.07	---	---	---	0.42*
			e5 <--> e7[7]		Noncog. Acti. <--> Cog. Acti.
			0.38		-0.20
					Cog. Assets <--> Cog. Acti.
					0.39
					Cog. Assets <--> Noncog. Acti.
					0.43

Table 36: Summary of Model Fits of Cognitive Reserve[8]

CR Factors	One factor model of CR	5 loading factors for CR.	One correlated error	4 loading factors for CR	3 factor models of CR.
CMIN	107.61	29.32	9.02	3.63	34.07

[6] * means that the regression weight was significant p<.05

[7] e5 is the error term of spirituality while e7 is the error term of PAQ.

[8] * p < .05

DF	20.00	5.00	4.00	2.00	16.00
CMIN/DF	5.38	5.87*	2.26	1.82*	2.13
GFI	0.82	0.92	0.98	0.99	0.95
AGFI	0.68	0.77	0.91	0.94	0.88
NFI	0.48	0.77	0.93	0.96	0.84
RFI	0.27	0.53	0.82	0.89	0.71
IFI	0.53	0.80	0.96	0.98	0.91
TLI	0.31	0.58	0.89	0.95	0.82
CFI	0.51	0.79	0.96	0.98	0.90
RMSEA	0.17	0.18	0.09	0.07	0.09

5.2.6. Hypothesis Five

Pearson correlation was employed to determine the degree of relationship between cognitive functions and indicators of cognitive reserve. The cognitive function measures that were included in this analysis were executive functions (i.e., the total score of the four conditions of the Stroop Color Word Interference Test and of the Design Fluency Test); attention (i.e., the raw score of the TMT-B, Digit Span and Letter Number Sequencing); memory (i.e., the score of immediate memory, long-term memory, and recognition of the RAVLT and the RCFT); language (i.e., score of Vocabulary of the WASI II, total score for FAS and Animals); Speed of Information Processing (i.e., the score of TMT-A and Coding subtest of the WAIS-IV); and Visuospatial skills (i.e., the score of copy RCFT and Block Design of the WAIS-IV). The cognitive reserve measures that was included was CR factor that includes premorbid intelligence (i.e., the raw score of the FSIQ-2 of WASI-II), education (i.e., years of education and score of health literacy), and the self-report questionnaire on spirituality and religiousness), occupational attainment (i.e., Prestige score). There were significant correlations between CR factor and RCFT LTM (-.16, p= .049), TMT-A (.23, p= .005), RAVLT Recall (-.17, p= .040), RAVLT

LTM (-.19, p= .022), and FAS (.21, p= .010) (See Table 37). Table 37 presents correlations between CR-factor and different cognitive function measures.

Table 37: Correlations Between CR-factor and Cognitive Functions[9]

Measures	Cognitive Reserve Factor **r**
Cognitive Reserve Factor	1
Immediate Visual Memory (RCFT Immediate Raw Score)	-0.09
Long Term Visual Memory (RCFT Delayed Raw Score)	-.16*
Visual Recognition (RCFT Recognition Raw Score)	-0.06
Time to Copy	0.08
Trail Making Test A (TMT A) Raw Score	.23**
Trail Making Test B (TMT B) Raw Score	0.02
WASIFSIQraw	.71**
WAIS-IV Block Design Raw Score	0.14
WAIS-IV Digit Span Raw Score	0.14
WAIS-IV Letter Number Sequencing Raw Score	0.14
Immediate Auditory Verbal Memory (RVALT Immediate Raw Score)	-0.12
Recall Auditory Verbal Memory (RAVLT Recall raw score)	-.17*
Long Term Auditory Verbal Memory (RVALT Delayed Raw Score)	-.19*
Auditory Verbal Recognition (RVALT Recognition Raw Score)	-0.06
FAS Raw Score	.21*
Animal Raw Score	-0.10
D-KFES Stroop Conditions 1 Word Raw Score	0.12
D-KFES Stroop Conditions 2 Color Raw Score	-0.07
D-KFES Stroop Conditions 3 Inhibition Raw Score	0.06
D-KFES Stroop Conditions 4 Inhibition/Switching Raw Score	0.03
D-KFES Design Fluency Condition 1 Raw Score	0.12

[9] * p<.05, **p<.01

D-KFES Design Fluency Condition 2 Raw Score	0.12
D-KFES Design Fluency Condition 3 Raw Score	0.08
WAIS-IV Coding Raw Score	-0.04

5.2.7. Hypothesis Six

Hierarchical multiple regression analyses were utilized to determine whether cognitive reserve (i.e., CR factor: IQ, years of education, occupational prestige, spirituality score) moderated the association between blood pressure group (BP) and the cognitive function factor score. Thus, the dependent variable was the cognitive function factor score and the predictors were cognitive reserve factor score, age, BP, the interaction between blood pressure group (BP x Age). Cognitive reserve factor score, age, the interaction between blood pressure group (BP x Age), and blood pressure (BP) were entered in step 1 as control variables. The interaction between CR factor and BP (CR x BP) was entered in step 2 as a test of moderation of the impact of BP on cognitive functions. Results of this hierarchical multiple regression analysis indicated that Cognitive reserve (CR factor) did significantly moderate the association between hypertension and cognitive functions, $\Delta R^2 = 0.02$, $F(5,140)$, = 36.598, p=. 026. The complete model accounted for 56.7 % of the variance of cognitive function but the moderation effect was 2%. However, there was an age group difference in CR factor score between normotensive and hypertensive participants. This moderation effect of CR is presented in Figures 10 and 11 which show greater neuroprotective effect among normotensive and hypertensive participants with high CR older than 72.5 years (See Figure 13) than among those younger than 72.5 years old (See Figure 12). A summary of the regression model is presented in Table 38 and regression coefficients for each predictor are presented in Table 39.

Table 38: Hierarchical Regression Analysis Summary for CR as Moderator Between HTN and Cognitive Functions

Step	R	R^2	R^2adj	ΔR^2	Fchg	P	df1
1. CR factor, age, BP & BP*age	0.74	0.55	0.54	0.55	43.23	0.00	4
2. CR x BP	0.75	0.57	0.55	0.02	5.07	0.03	1

Table 39: Regression Analysis Summary for CR as Moderator Between HTN and Cognitive Function

Variable	B	β	T	p
1. BP	1.84	0.72	2.56	0.01
2. Age	-0.04	-0.58	-5.41	0.00
3. CR factor	0.09	0.09	0.98	0.33
4. BP1 x age	-0.03	0.01	-2.59	0.01
5. CR x BP	0.28	0.21	2.25	0.03

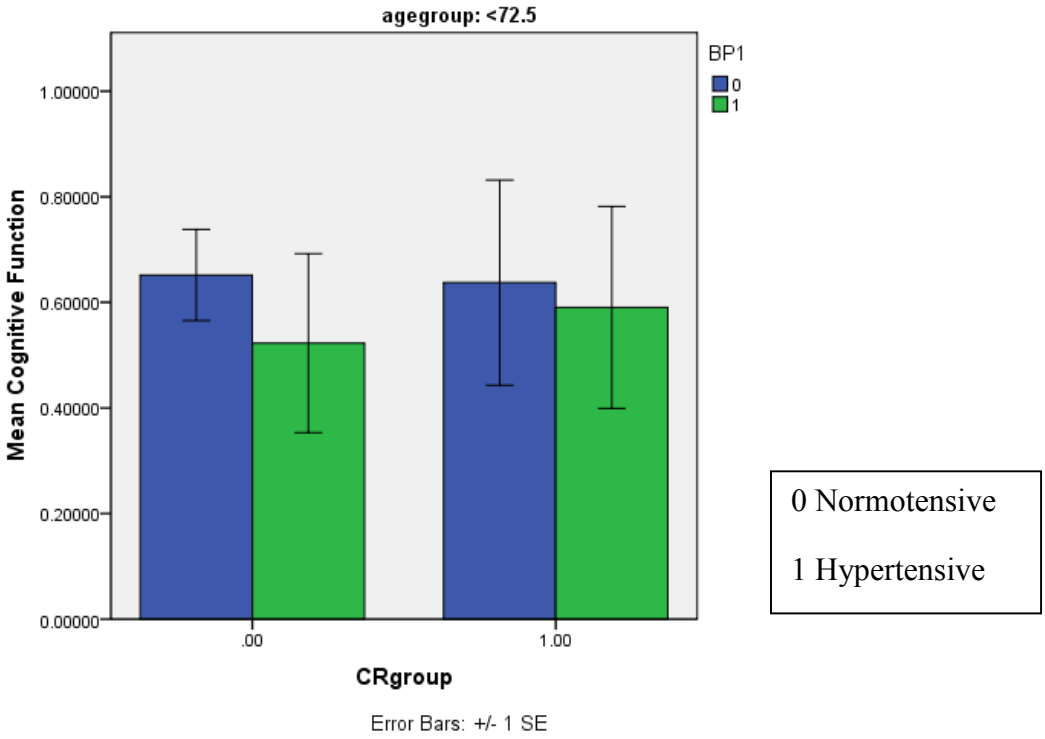


Figure 12: CR Moderation Effect Among Participants Younger than 72.5yrs

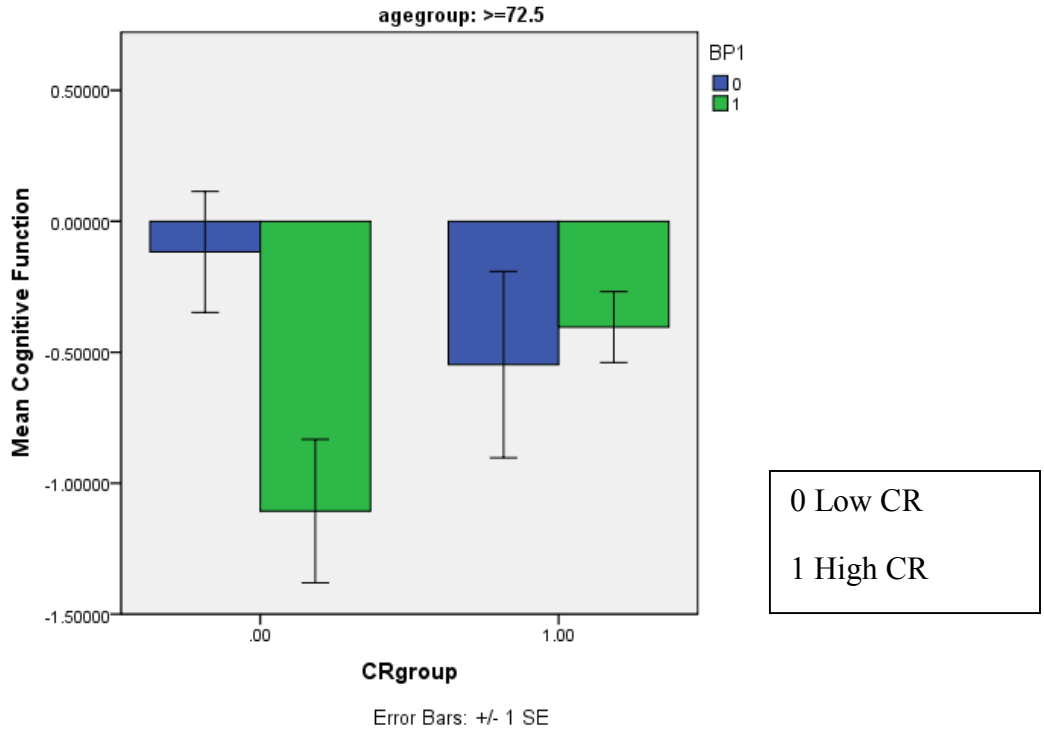


Figure 13: CR Moderation Effect Among Participants Older than 72.5yrs

5.2.8. Hypothesis Seven

A One-way between participants Multivariate Analyses of Variance (MANOVA) were conducted to assess whether there were statistically significant means differences in cognitive functions among hypertensive participants divided into two groups: (1) controlled or uncontrolled; (2) those with a shorter (10 years or less) or longer duration of hypertension (more than 10 years) as measured by the number of years since the diagnosis. The cognitive functions measures that were included in this analysis were executive functions (i.e., the total score of the four condition of the Stroop Color Word Interference Test and of the Design Fluency Test); attention (i.e., the raw score of the TMT-B, Digit Span and Letter Number Sequencing); memory (i.e., the score of immediate memory, long-term memory, and recognition of the RAVLT and the

RCFT); language (i.e., the score of Vocabulary of the WASI II, total score for FAS and Animals); Speed of Information Processing (i.e., the score of the TMT-A and Coding subtest of the WAIS-IV); and Visuospatial skills (i.e., score of copy the RCFT and Block Design of the WAIS-IV). Control of hypertension is a dichotomous variable indicating whether or not a participant has controlled or uncontrolled hypertension. Duration of hypertension in years was a continuous variable.

In terms of the first part of this hypothesis, the MANCOVA was not conducted because they were only 22 participants in the group of those with uncontrolled hypertension. Therefore, ANCOVA was utilized to determine the effect of uncontrolled hypertension on cognitive functions (i.e., the cognitive function factor score) while controlling for age. There was a significant effect of uncontrolled hypertension on cognitive functions while controlling for age, $F(2,89)=40.80$, $p<.0001$. The whole model (i.e., age and uncontrolled hypertension) accounts for 49% in cognitive function (R^2 or partial eta squared= .49). However, age accounted for 44% of the variance in the cognitive function ($R^2= .44$) while uncontrolled hypertension accounted for 5% ($R^2= .05$).

A second ANCOVA was conducted to determine the effect of duration of hypertension on cognitive functions (cognitive function factor score) while controlling for age. In the first part of this analysis, the duration of hypertension provided by the RN was utilized. There was a significant effect of the duration of hypertension on cognitive function after controlling for age $F(2,41)=8.70$, $p=.04$. The complete model (i.e., age and duration of hypertension) accounted for 31% ($R^2= .31$) of the variance of cognitive functions, in which age accounted for 31% ($R^2= .31$) and the duration of hypertension for 11% ($R^2= .11$). In the second part of this analysis, the

duration of hypertension provided by the participants was used. There was no significant effect of duration of hypertension on cognitive function while controlling for age $F(2,59)= 20.76$, p= .29.

5.3. Secondary Analyses

5.3.1. Impact of Hypertension on Specific Cognitive Functions

Factor scores were created for each participant using the PCA with orthogonal rotation, forcing the number of factor to one for each cognitive function. Analyses were conducted to determine the effect of hypertension on specific groups of cognitive functions based on factor scores and previous literature, while controlling for age and the interaction between age and blood pressure. These groups were executive functions, measured by PCA factor scores of the four condition of the Stroop Color Word Interference Test and of the Design Fluency Test); attention by factor score of the TMT-B, Digit Span and Letter Number Sequencing; memory by the factor score of immediate memory, long-term memory, and recognition of the RAVLT and the RCFT; language/verbal fluency by the factor score for FAS and Animals; Speed of Information Processing by the factor score of the TMT-A and Coding subtest of the WAIS-IV; and Visuospatial skills by the factor of score of copy raw and copy time of the RCFT and Block Design of the WAIS-IV. There were significant differences in means between normotensive and hypertensive participants after controlling for age and the interaction between blood pressure and age in executive functions $F(3, 142)=8.03$, $p<.0001$, $R^2= .145$); attention $F(3,142)=21.66$, $p<.0001$, $R^2= .31$); memory $F(3, 142)=33.92$, $p<.0001$, $R^2= .42$); visuospatial abilities, $F(3, 142)=15.25$, $p<.0001$, $R^2= .24$); Speed of information processing, $F(3, 142)=40.58$, $p<.0001$, $R^2= .462$); and Verbal fluency, $F(3, 142)=10.79$, p= .000; $R^2= .186$).

5.3.2. Moderation Effect of CR on the Impact of Hypertension on Specific Cognitive Functions

Hierarchical multiple regression analyses were utilized to determine the moderation effect of CR on the association blood pressure (BP) and each cognitive function (i.e., memory, executive functions, attention, speed of information processing, visuospatial abilities, and verbal fluency). The dependent variable was the factor score of each cognitive function and the predictors were CR factor score (i.e., WASIFSIQ, years of education, occupational prestige, spirituality score), age, blood pressure, interaction between blood pressure and age (BP x Age). CR factor score, age, blood pressure, interaction between blood pressure and age (BP x Age) were entered in step 1 as control variables. The interaction between CR factor and BP (CR x BP) was entered in step 2 as a test of whether CR moderates the impact of BP on cognitive functions. Results of these hierarchical multiple regression analyses indicated that Cognitive reserve (CR factor score) significantly moderated the relationship between hypertension and memory, ΔR^2 = .02, $F(1,140)$, = 26.25, p=. 031. This complete model accounts for 45 % of the variance in the protection of cognitive function while moderation effect of CR on memory was 2%. A summary of the hierarchical regression analysis of the moderation by CR between the association of BP and memory is presented in Table 40. In addition, regression coefficients between each predictor and the dependent variable are presented in Table 41.

Table 40: Summary of the Regression Model

Step	R	R^2	R^2adj	ΔR^2	Fchg	P	df1
1. CR factor, BP, age, BP*age	0.65	0.43	0.41	0.43	26.25	0.00	4
2. CRxBP	0.67	0.45	0.43	0.02	4.75	0.03	1

Table 41: Regression Coefficients Between Each Model and Memory

Variable	B	β	T	p
1. BP	2.09	1.02	2.58	0.01
2. Age	-0.03	-0.45	-3.680	0.00
3. CR factor	0.07	-0.07	-.67	0.51
4. BP1 x age	-0.03	-1.13	-2.54	0.01
5. CR x BP	0.30	0.22	2.18	0.03

However, the results of other hierarchical multiple regression analyses did not indicate a significant moderation effect of cognitive reserve (CR factor) on the relationships between hypertension and executive functions, R^2= .162, ΔR^2 =. 015, $F(1,140)$, = 5.43, p=. 120; attention, R^2= .435, ΔR^2 =. 01, $F(1,140)$, = 21.58, p=.118.; speed of information processing, R^2= .478, ΔR^2 =.001, $F(1,140)$, = 25.64, p=. 670; visuospatial abilities, R^2= .303, ΔR^2 =. 01, $F(1,140)$, = 12.17, p=. 257; and verbal fluency, R^2= .261, ΔR^2 =. 001, $F(1,140)$, = 9.90, p=. 220.

CHAPTER 6: DISCUSSION

This section describes the findings of this study and reports the results of each hypothesis. Limitations and clinical implications of this study will be briefly presented. Additionally, recommendations for future research will be made. Finally, a conclusion will summarize the study.

6.1. Findings

This study is the first to examine the moderation effect of cognitive reserve (CR) on the impact of hypertension on neurocognitive performance of retired priests and nuns as well as very active lay participants. To investigate this moderation effect, initial analyses were conducted to examine whether all the neuropsychological assessments used evaluate a single dimension of neurocognition and whether hypertension is associated with variation in neurocognition. In addition, we also investigated whether CR factors load into one factor that could be called cognitive reserve. Then, the question of moderation by CR could be addressed.

Regarding the first hypothesis which investigated whether cognitive function indicators clustered together to measure the same construct that could be called cognitive function, current findings supported this hypothesis. The results of this study revealed that different neuropsychological assessments (i.e., executive functions, attention, memory, visuospatial abilities, speed of information processing, and language) used in this study measure something in common, which will be called neurocognitive function. Therefore, assessments used in this study significantly constitute a battery of neuropsychological tests that evaluate the different neurocognitive functions. In this sense, these findings support the importance of the “standard battery approach” championed by Halstead (1947) and Reitan (1966) as one of the useful

approaches for neuropsychological assessments in evaluation of all the cortical functions as one. Our results revealed that this one-factor model of cognitive function was poor, however, because some fit indices fell below .90. The weakness of this one-factor model can probably be explained by the disadvantages of battery approach, which is time consuming and requires much effort by both the participant and the examiner and sometimes does not explain poor performance of a participant in a specific cognitive function area. (Zillmer, Spiers, & Culberton, 2008). White and Stern (2003) believed that the theoretical foundation of a neuropsychological battery is embodied in the combination of both empiricism (i.e., clinical prediction as primary goal) and cognitivism (i.e., neuropsychological constructs and clinical prediction as second). This one factor model of neurocognitive function explained the existence of neuropsychological batteries such as NAB, RBANS, Reitan, CANTAB, Dean Woodcock Neuropsychological assessment, and Luria-Nebraska neuropsychological battery.

The second and third hypotheses assessed the significance difference in the means of cognitive functions between normotensive and hypertensive participants after co-varying for age and the interaction between blood pressure and age. Current results supported these two hypotheses. These findings are consistent with previous studies have related poor performance in cognitive function to the association between hypertension and atherosclerosis (i.e., hardening of the arteries) which, in turn, leads either to lacunar infarction or to lacunar stroke over years (Lammie, 2000). These vascular changes have been related with structural changes in the frontal, temporal, and occipital lobes (Gold, et al., 2005; Den Heijer, et al., 2004; Raz & Rodriguez, 2003) as well as in the hippocampus, amygdala, anterior cingulate, and thalamus involved in neurocognition performance. A number of studies have reported neurocognitive decline in

hypertensive participants (Joas, et al., 2013; Power, et al., 2011; Novak & Hajjar, 2010, Duron & Hanon, 2008, Waldstein, 1995) and this decline has been found to be slow and progressive (Cherubini, et al., 2010). In this study, poor performance in neurocognitive assessments was associated with systolic hypertension, as has been found by other previous researchers (Kuo, et al., 2004; Seux, et al., 1998; Kilander, et al., 1998). Consistent with previous hypertension literature, we found poor performance among hypertensive participants in cognitive functions such as executive functions (Vicario, et al., 2005 & Elias, et al, 2004), attention (Shehab & Abdulle, 2011 & Knecht, et al., 2009), memory (Shehab & Abdulle, 2011; Brady, et al., 2005 & Saxby, et al., 2003); speed of information processing (Bucur & Madden, 2010 & Knecht et al., 2009); verbal fluency (Elias, et al., 1995 & Kuusisto et al., 1993); and visuo-spatial skills (Thorvaldsson, et al., 2011 & Brady, et al., 2005). These poor performances in neurocognitive measures were found to be greater especially among hypertensive participants older than 72.5 years old.

In the sample tested here, most antihypertensive drugs enhanced the control of hypertension (Khan, et al., 2005). Additionally, our findings are consistent with some major studies which did not find a protective effect of antihypertensive drugs in preventing poor neurocognitive performance (e.g., the Hypertension in the Very Elderly Trial of Peter et al., 2008; the Prevention regimen for Effectively Avoiding Second Stroke study of Diener, et al., 2008; The Study of Cognition and Prognosis in the Elderly, 2003; the Systolic Hypertension in the Elderly Program Study of Applegate, 1996; and Medical Research Council's study by Prince, et al., 1996). The ineffectiveness of antihypertensive drugs in the protection of cognitive functions has been explained in the hypertension literature by noting that these drugs are mostly

intended to prevent dangerous cardiovascular events rather than protecting against cognitive decline (Kaplan & Victor, 2010). Kaplan and Victor (2010) have also associated the lack of neuroprotective effects of antihypertensive drugs to the silent course of progression of hypertension which results in a typical delay in its treatment. This indicates that sometimes it is "too little, too late" when individuals become aware of their hypertension and start getting the appropriate treatment to control it. Finally, Novak and Hajjar (2010) have pointed out that the specific mechanisms of actions of antihypertensive drugs play important roles in the protection of cognitive functions. Therefore, some antihypertensive drugs have been found to better control hypertension than others and controlled hypertension has been found to have neuroprotective effects.

Along this line of reasoning, this study has demonstrated that uncontrolled systolic hypertension is associated more with poorer neurocognitive performance, compared to those with controlled hypertension. These results support the first part of our hypothesis 7 which predicted significant mean difference in cognitive functions between participants with controlled and uncontrolled hypertension. Present findings are consistent with previous studies which reported poorer neurocognitive performance among those with uncontrolled than those with controlled hypertension (Brady, et al., 2005 & Vicario, et al., 2005). The current study has also found some exogenous factors associated with uncontrolled hypertension such as being younger than 72.5 years old, having a long duration of hypertension (i.e., more than 10 years), low cognitive abilities, low CR, low spiritual and religious behaviors, and few physical activities. In addition, our results showed that the group with uncontrolled hypertension were less likely to be

involved in DASH, sodium intake reduction and weight reduction, as well as in reduction of lipid and in moderation of alcohol intake.

Concerning the second part of Hypothesis Seven, which predicted significant mean difference in cognitive functions in participants with a shorter (i.e., 10 years or less) or longer duration (i.e., 10 years or more) of hypertension, the present study found conflicting results. The duration of hypertension provided by the nurse had negative correlation with performance in cognitive functions in hypertensive participants, with longer duration being associated with poorer performance. The duration recorded by the participants themselves, however, did not demonstrate a significant relation with cognitive performance. Tzourio and his colleagues (1999) reported a correlation between the duration of hypertension and cognitive decline while other researchers have emphasized that it is mostly hypertension with a duration of more than 10 years that leads to cognitive decline (Waldstein, 1995, 2003). The positive findings can be interpreted with a hypothesis that longer duration of hypertension has a deleterious impact on the brain structures involved in neurocognition.

This study explored the moderation effect of cognitive reserve against the deleterious impact of hypertension on neurocognition. The current study tested moderation statistically as an interaction effect. In order understand the potential moderation role of CR, we examined whether all the predictors selected (e.g., Parent SES, FSIQ, years of education, occupational prestige, health literacy, spiritual and religious behaviors, cognitive and physical activities) cluster into one factor called a "cognitive reserve construct." The current study did not support the synergistic use of all these CR proxies as one construct called CR. Our findings demonstrate that four CR proxies (i.e., FSIQ, years of education, occupational prestige, and spirituality) cluster to

one construct, which is called cognitive reserve in this dissertation. In addition, other analyses tested a three-factor model of CR, which includes cognitive assets (FSIQ, years of education, and occupation prestige), noncognitive activity (Health literacy, Spirituality, and physical activity), and cognitive activities (Health literacy, Cognitive activities, and Parent SES). Moderation analyses used the first model of the CR construct, which included cognitive assets and one predictor of the non-cognitive activities, that is, spiritual and religious behaviors. A significant moderation effect of CR, defined as educational attainment, occupation, and estimated IQ has been reported previously by study on the detection of mild cognitive impairment and dementia in high-functioning individuals (Tuokko, et al., 2003). Shapiro and colleagues (2014) has recently reported the moderation role of CR against apathy in individuals with Human Immunodeficiency Virus using the composite of years of education and estimation of IQ from word-reading ability WTAR.

The CR construct used here, as the combination of cognitive assets with spirituality and religious behaviors is a new finding from our confirmatory factor analysis. It is important to indicate that the contribution of spiritual and religious behaviors to CR construct is not generalized to all spiritual and religious aspects but only active participation in prayer, mediation, contemplation, and attendance at religious services. It could be hypothesized that being active with spiritual and religious behaviors serves as a neuroprotective factor. For instance, MacDonald and colleagues (2002) have reviewed various studies that support the physical and neurological impacts of meditation. Other investigators have found that intense prayer, contemplation, and meditation changed numerous structures and functions in the brain (Newberg & Waldman, 2009).

The current findings of the one factor model with four predictors of CR are consistent with CR literature. Stern (2009) pointed out that measures of CR proxies have been used in various studies either separately or synergistically. Some studies have used a single proxy of CR such as parent SES (Richard, et al., 2007); education (Stern et al., 2012, Garibotto, et al., 2012, Fourbert-Sanier, et 2012, Craik, et al, 2010, Tucker-Drob, et al, 2009, & Valenzual & Schdev, 2005); IQ (Stern, 2009); occupation (Ghaffar, Fiati, & Feinstein, 2012, 2009; Sole-Padulles, et al, 2009; Staff, et al., 2004); physical activities (Gow, et al. 2012, Varela, Ayan, Cancela, & Martin, 2011); and leisure activities (Ruiz-Contreras, et al., 2012, Marioni, et al. 2012, Reed, et al., 20121, Suchy, et al., 2011). Estimated IQ has been used as a proxy of CR in AD and mild cognitive impairment studies (Stern, et al., 2009 & Tuokko, et al., 2005). Additionally, studies have measured CR as one factor abstracted from different proxies (Shapiro, et al., 2014, Stern, et al., 2009). Nucci and his colleagues have evaluated the moderation role by measuring CR with a Cognitive Reserve Questionnaire Index (CRiq), which includes three proxies of CR: education, working activities, and leisure activities. Stern (2012) suggested that CR be measured using challenging assessments that are more specific for a particular neuropathology and the use of associative learning and crystallized measures. Our factor-analytic findings suggest that IQ, occupational prestige, years of education, and spiritual and religious behaviors could potentiality be considered as preliminary proxies of a CR construct. However, some measures which were expected to reflect CR did not correlate with cognitive function (e.g., cognitive and physical activities). These findings could be explained by memory lapses related with self-report measures and difficulties experienced by participants in filling out these measures.

These findings suggest a protective effect of CR (i.e., a factor score based on FSIQ, years of education, occupational prestige, and spirituality) against poor neurocognitive performance in participants with clinical hypertension, particularly in older participants with a longer duration of uncontrolled hypertension. While previous literature has demonstrated that some proxies of CR, for example high education, occupation (Davila, et al., 2012), spirituality and religious activities (Bell, et all, 2012, Chung, et al., 2012, Sorensen, et al., 2011), help in the control of hypertension, this is the first study, to our knowledge, to specifically evaluate the relationship between CR and poor neurocognitive performance in mostly elderly population with clinical hypertension.

Additionally, consistent with previous CR literature, we found higher neurocognitive performance in participants with high CR than in those with low CR after controlling for the effect of age, blood pressure and age. The effect of blood pressure, age, and CR was 55% on cognitive function ($\Delta R^2 = .55$). The neuroprotection effect of CR on cognitive functions accounted for 2% of the variance in cognitive function. Taken together, these results support the theory that hypertensive individuals with higher CR can withstand the deleterious impact of hypertension on cognitive functions slightly better, particularly in older individuals. Subsequent analyses revealed that a moderating role of CR was more significant in memory measures than in other cognitive functions.

Several studies have shown that higher levels of intelligence, education, and occupational attainment (i.e., CR) are good predictors of an individual's ability to cope with neuropathology, resulting in fewer deficits in neurocognitive functions (Scarmeas & Stern, 2003; Stern, 2002, 2009, 2011). Various studies have found a protective effect of CR in Alzheimer's disease (Stern,

2009; Valenzuela & Schadev, 2006), Parkinson's disease (Glat, et al., 1996), HIV dementia (Farinpour, et al., 2003) traumatic brain injury (Kesler, et al., 2003), schizophrenia (Barnett, et al., 2006), vascular injury (Elkins, et al., 2006; Dufouil, et al., 2006), and coronary artery disease. However, studies regarding the moderation effect of CR in hypertension are relatively few. This neuroprotective role of CR in hypertension has been underestimated and less studied presumably because initial studies did not find a significant effect of hypertension on cognitive functions (Vasilopoulos, et al., 2012, Vicario, et al., 2011; Saxby, et al., 2003). In addition, the difference in means between normotensive and hypertensive participants has been estimated as a small effect size (i.e., d= .30). This present study has found poorer performance in neuropsychological measures as well as a protective effect of CR in participants with clinical hypertension.

This study has also shown that there is a trade-off between high CR and clinical hypertension. Participants who were highly educated with managerial occupations and who had high IQ as well as high spiritual and religious behaviors (i.e., high CR) had a high frequency of hypertension. When two subgroups were compared (i.e., high versus low CR), the high CR subgroup was found to have a higher frequency of controlled hypertension and higher cognitive performance. In this line, this study revealed a moderating effect of CR on cognitive functions in individuals with clinical hypertension. There are three possible explanations for this relationship between CR and cognitive functions in our study. First, it may be, as suggested by Tucker and Stern (2011), that high CR individuals were using efficient processing mechanisms and compensatory cognitive networks. Second, it could be argued that individuals with high CR use alternative cognitive strategies and were involved in many determinant factors contributing in the control of their hypertension. Finally, individuals with high CR might tolerate a high impact of

hypertension and its deleterious consequences on the brain. It is possible that high CR has contributed to greater learning ability through a participant's lifespan, strengthened connections between neurons, and resulted in greater synaptic plasticity, adult neurogenesis, and other neurophysiological changes.

6.2. Limitations

There are some limitations to this study in terms of internal and external validity. Ideally, a longitudinal clinical trial of cognitive reserve is needed to infer a causal relationship, that CR is neuroprotective against cognitive decline in the face of neuropathology. A cross-sectional study can only show association, not causality. Further, in terms of internal validity, it is important first to point out issues related to unknown confounding variables in the relationship between clinical hypertension as independent variable (IV) and neurocognitive performance measures as dependent variables. This indicates that there could be some confounding variables related to the duration, awareness, treatment, and control of hypertension. Related to the history of hypertension, studies have shown that there is sometimes a time lapse between beginning of hypertension and the awareness of the condition. Hypertensive individuals sometimes discovered their state of hypertension significantly later than when the disease started. This explanation can explain the different duration reported by the participants and the registered nurses. Because different medications and diagnoses of participants were classified, this study may have not included some important interactive effect of some of these medications and some deleterious impacts of some past or present diseases on participants' neurocognitive performance. For example, some participants may have had some disease (e.g., depression, stroke, aneurism, seizures, epilepsy, sleep disease, depression, and anxiety disorders) and taken medications (e.g.,

addictive drugs, antidepressants, muscle relaxants, narcotics, chemotherapy, and hormone therapy), or abused some substances (e.g., alcohol, cocaine, opiates) in the past which may not have been reported or included in their medical histories.

The second limitation could be the fact that many of the constructs used in this study were latent, which led to the use of observed variables for analyses. Latent trait analysis and directional modeling would be better approach to analyse the data. Additionally, it would have been better to use the participants' premorbid IQ to predict their cognitive reserve. However, this study used participants' IQ to predict their cognitive reserve. In this sense, some measures of IQ and cognitive reserve may have been high intercorrelated.

The third limitation to this study could be the influence of selection bias. This sample was a sample of convenience, presenting an issue of volunteerism. Many of the participants interested in this research were Christians, priests and nuns, and highly religious and spiritual because the investigator's identity as a priest may have influenced individuals to volunteer. Additionally, some participants may have volunteered because they were concerned about the decline of their neurocognitive condition and wanted to be assessed. Others may have volunteered because they knew they were very skilled intellectually and very healthy.

Other limitations to this investigation are testing familiarity and attrition. Some participants reported during the assessment that they have been already evaluated with some of the measures used by this neuropsychological core battery of this research. Some participants indicated that they participated in the Rush Hospital Study for Alzheimer's disease for priests and nuns at Chicago, Illinois. Others regularly take some of the assessments through the Lumosity software programs (i.e., brain training games to improve cognitive abilities) and others

have been tested by their neurologists and neuropsychologists. Additionally, some participants expressed difficulties in filling out the Physical Activities Questionnaire (PAQ) and could not remember their leisure activities at their early stage of life. Another limitation is the imperfect measurement of some characteristics, for example, spiritual and religious behaviors, cognitive and physical activities, and years of education. For instance, this study operationalized education in terms of total number of years in school starting from elementary until graduate school. This definition of education takes into account education as a quantity in years but not as a quality. Although it is difficult to measure quality of education, it may be the more important aspect. Finally, some participants did not complete all the required evaluations due to reasons related to health, age, and other issues.

There are some limitations related to the generalizability of this study. Although this study can be generalized mostly in the context of those individuals over 72.5 years, priests and nuns, some issues pertain to its generalizability to the whole population. First, in terms of population generalizability, this sample was mostly comprised of Caucasians, highly educated, older priests and nuns, Christians, and highly religious and spiritual participants. There was less diversity in terms of race, level of education, religion, level of income, type of occupation, and parents' socio-economic status. For instance, more diversity in terms of religion and status could have share light on the association of spiritual and religious behaviors as one of the proxy of CR in this study. Generalizability would have been improved with a larger sample size, which takes into account the small effect size of hypertension on the neurocognitive performance.

The second limitation of generalizability is the timing of the study. The formulation of the hypotheses and the understanding the concept of hypertension, its management, and

treatment were formulated following the Seventh Report of the Joint National Committee (JNC-7, 2003) treatment algorithm and guidelines. For example, JNC- 7 designated hypertension when the patient has three readings of blood pressure above 140/90 mm Hg. The new hypertension guidelines management algorithm of JNC-8 (2014) makes a clear distinction in the understanding of blood pressure for an individual before 60 years old and above 60 years. For these new recommendations, the blood pressure goal for a person younger than 60 years old without diabetes and chronic kidney disease is to maintain the SBP less than 140 mm Hg and DBP less than 90 mm Hg. For individuals over 60 years old without diabetes and chronic kidney disease, the experts of JNC-8 recommend a systolic goal of less than 150 mm Hg and diastolic goal of less than 90 mm Hg. Therefore, it could be argued that some of the participants over 60 years old without diabetes and chronic kidney disease who were classified in this present study as hypertensive would not be categorized today in the light of JNC-8.

Other limitations of this study include the use of self-report measures, fatigue, and motivation. Concerning the disadvantages of self-report measures, it has been found that these measures can lead to exaggeration, embarrassment about revealing private details, and social desirability bias. Self-report measures can also be affected by memory lapses and by the participant's feelings at the time of filling out the questionnaire. Finally, fatigue and poor motivation may have impacted on this elderly population due to the length and complexity of assessments.

6.3. Clinical Implications

Despite these limitations, this investigation of the neuroprotective role of the CR in individuals with hypertension may provide relevant information about clinical assessment,

remediation, and prevention of clinical hypertension. Applying the clinical proposals from Stern (2012), the results of this study indicates that clinical assessments of CR might offer valuable diagnostic and therapeutic assets for hypertensive participants with high CR. First, neuropsychological assessments of hypertensive individuals with high CR may require clinicians to use more challenging and sensitive measures to determine which scores could serve as bio-cognitive markers in detecting deleterious effects of clinical hypertension on the brain and also in grading cognitive stages of the disease. Along these lines, CR could be utilized secondly as a factor that may affect the rate of cognitive decline, the stage of clinical hypertension, and the diagnosis of vascular dementia related to hypertension.

Concerning the possible application of the CR construct in remediation and prevention of cognitive decline in individuals with clinical hypertension, this study may support epidemiological and clinical evidence emphasizing the benefits of cognitive activities. Targeting specific cognitive functions, strategies to possibly remediate and compensate executive functions might include modifying one's environment, and routinizing daily activity as well as using mnemonic strategies, being exposed to challenging tasks, planning ahead, and using computerized techniques (Callahan, 2009). In terms of attention, Levitt and Johnstone (2009) might suggest reducing distracting stimuli in the environment, and structuring activities, and planning short activities and frequent breaks as remediation tips. The Mayo Clinic has proposed seven steps to improve memory, which include staying mentally active, socializing regularly, getting organized, eating a healthy diet, exercising regularly, and managing chronic conditions (Creagan, 2006). Additionally, strategies for cognitive rehabilitation of memory might include the restoration technique (e.g. repeated practice for word-list learning), reorganization techniques

(e.g., visualization skill learning), and behavioral compensation (e.g. using a memory notebook, organizers, and to-do lists) (Skeel & Edwards, 2009).

Doing any activity faster than expected, such as playing musical instruments (e.g., keyboard, guitar, and organ) and writing letters or e-mails by typing on a computer keyboard has been found to increase speed of information processing and visual scanning. Playing sudoku, crossword puzzles, logic puzzles, and fast-paced card games are considered as strategies to process information faster. Challenging oneself to quickly find telephone numbers in a directory, locate a word in a glossary/index or counting coins are activities that maintain speed of information processing. Additionally, giving oneself time limits to read or write a text and scanning or reviewing the next paragraph to be read are important strategies in maintaining speed of information processing. Finally, computer games, video-games, and any exercise which involves muscle activation could improve speed of information processing. Shaw (2009) has recommended strategies such as scanning training, mapping, reducing the number of stimuli, and playing interactive video games as well as drawing, building, copying, and following step by step instructions. Finally, using measuring tools, calculating spatial relationships, writing and reading directions, using landmarks, and tracing map routes have been recommended as strategies to improve spatial orientation and body schema skills (Shaw, 2009).

The current study supports the viewpoint that considers the brain as one of the body's muscles that requires daily and weekly workout schedules in order to develop cognitive fitness and cope with normal aging and neuropathology (Hurley, 2013). Lumosity (i.e., the brain training website with 50 million subscribers), Happy Neuron of Mountain View, Cogmed (a British education program), Neuronix (an Israeli program) are among the well-known brain

programs of the "cognitive fitness gymnasiums" (New York Times, March 11, 2014). Involvement in religious and spiritual activities (e.g., prayer, meditation, contemplation, and yoga) constitutes one important cognitive workout for strengthening one's brain. Some of these brain workouts have gained public support mostly for children with ADHD, individuals with different types of dementias, patients with traumatic brain injury, HIV, and some psychiatric diseases. Along these line, the present study supports use of some of the personalized and computerized brain workouts despite some conflicting findings about these cognitive training tools (New York Times, March 11, 2014). Additionally, the current study's findings are consistent with scientific evidence that brain workouts are a beneficial part of treatment and management of the deleterious cognitive impacts of hypertension, which affects over one third of the world population and 66.7% of the U.S. population of adults from over 60 years and over. Finally, brain workouts may be an important adjunct to the pharmacological management (i.e., antihypertensive drugs) and for the protection of cognitive function in individuals with hypertension.

6.4. Suggestions for Future Research

In the light of these limitations and findings, future research could use neuroimaging studies to examine how high CR individuals draw passively on more efficient neural pathways and use accessory brain pathways to compensate pathways impacted by clinical hypertension. Using the brain reserve capacity model, future investigators can measure metabolic activities of the brain, neuronal number, synaptic number and density, brain volume, and white matter connections to understand a potential neuroprotection effect in individuals with hypertension.

The study of brain reserve capacity and emotional reserve capacity are needed because the present study investigated only the abstract construct of cognitive reserve.

It is imperative that future studies investigate the construct of cognitive reserve or brain reserve capacity in individuals with clinical hypertension by using the JNC-8 recommendations and hypertension guideline management algorithm. Such clinical research will require a large sample of participants that could contrast participants less than 60 years old with those of more than 60 years old who have neither diabetes nor chronic kidney disease (CKD). Ideally, a randomly selected sample would be comprised of participants from various ethnic groups, religions, occupations, and different durations of hypertension. Only then will we be able to understand much better the neuroprotective effect of CR in individuals with clinical hypertension.

There are other possible explanations for our findings about the protection of CR against poor neurocognitive performance in individuals with clinical hypertension. Although our analyses adjusted for many confounders (e.g., age, interaction of age and blood pressure, number of diagnoses and medications), it is likely that additional unmeasured confounders have not been identified. It could be argued that high CR participants with clinical hypertension were more involved in more cognitive activities than were low CR participants. Therefore, future studies on CR and cognitive functions in individuals with clinical hypertension should also examine a wider range of cognitive activities through pilot studies in order to know whether they are truly moderators. One of the proxies, which requires closer examination of its moderation role in the future CR literature, is spiritual and religious behavior.

As noted previously in the limitations, our investigation was a correlational study that used a cross-sectional design, which did not establish any causation between CR and cognitive function. Future research examining this association further or exploring possible causation between CR and neurocognition performance should conduct studies that utilize experimental and longitudinal designs. For example a true experimental design should include two groups, the experimental group (i.e., high CR condition) and the control group (i.e., low CR condition). Researchers could use a pretest-posttest design where participants with hypertension and without hypertension receive a pretest with a measure of cognitive functions and a posttest of the same measure. This design will help to determine a learning curve and how much each group has gained when exposed to cognitive training. This design can be used with neuroimaging to localize brain structures involved in efficient and compensatory approaches utilized when CR is increased. Finally, a longitudinal design could follow normotensive individuals for years to measure pre- and post-hypertension cognitive function score, such as Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) or Montreal Cognitive Assessment (MOCA), to assess the nature and the direction of the association between CR and cognitive function. Longitudinal studies can determine the point of inflection where individuals start noticing cognitive decline.

6.5. Conclusion

The current study investigated the moderation effect of cognitive reserve on the impact of clinical hypertension on performance in neurocognitive functions. The cognitive reserve (CR) construct has been defined as lifelong experiences (e.g. IQ, education, occupation, and leisure activities) which actively constitute a buffer for cognitive functions when an individual suffers a

certain neuropathology. To study this moderation role of CR, 150 participants including retired priests and nuns, and lay people were recruited from Illinois and Michigan. Cognitive reserve was assessed with parent SES, IQ, years of education, occupational prestige, spiritual and religious behaviors, health literacy, cognitive and physical activities. The operationalization of clinical hypertension was in the line with the Seventh Report of the Joint National Committee (JNC-7). Clinical hypertension was defined in terms of one of two conditions: (1) three consecutive positive readings of blood pressure of systolic high or equal to 140 and/or diastolic higher or equal to 90; (2) being treated with one or more antihypertensive drugs. Participants of this investigation were evaluated with the same sequence of a neuropsychological battery, which assessed their executive functions, attention, memory, visuo-spatial skills, speed of information processing, and verbal fluency. Participants completed self-report measures to provide demographic information, information about their leisure activities as well as, spiritual and religious behaviors. Registered nurses provided the participants' blood pressure readings and needed medical information.

Using a cognitive function-factor score combining the scores of 25 neurocognitive tests, the results of the present study demonstrated a significantly poorer performance in neurocognitive functions in individuals with clinical hypertension than in normotensive after controlling for their age, along with the interaction between age and blood pressure. Poor performance in neurocognitive functions in hypertensive individuals was most pronounced in participants with longer duration of hypertension (i.e., more than 10 years) or with uncontrolled hypertension. Comparisons between subgroups on every cognitive function revealed significantly poorer performance in executive functions, attention, memory, visuospatial

abilities, speed of information processing, and verbal fluency. Contrary to our hypothesis considering all the predictors of CR to cluster into one factor called CR construct, current findings showed that only four proxies of CR (i.e., IQ, years of educations, occupational prestige, spiritual and religious behaviors) clustered into a single factor, which we called CR. Other results presented a model with three different factors, which include cognitive assets, cognitive activities, and non-cognitive activities, but this model did not fit the data well. A CR-factor, combining the four predictors, significantly moderated the association between clinical hypertension and cognitive functions. These findings suggest a neuroprotective effect of CR against poor neurocognitive performance in individuals with clinical hypertension after a long duration of the disease or with uncontrolled disease.

The conceptual model of this study can be crafted differently in line with the present findings. Cognitive reserve factor would only include IQ, years of educations, occupational prestige, and spiritual and religious behaviors. These predictors were found to cluster into one factor while other proxies did not significantly fit the CR factor. In terms of covariates, only age was found to have significant effect on the cognitive functions in those with clinical hypertension. Due to small size effect of hypertension on language abilities, this study assessed only verbal fluency rather than all language components. Therefore, the new conceptual model of this study would be represented as follows in Figure 14.

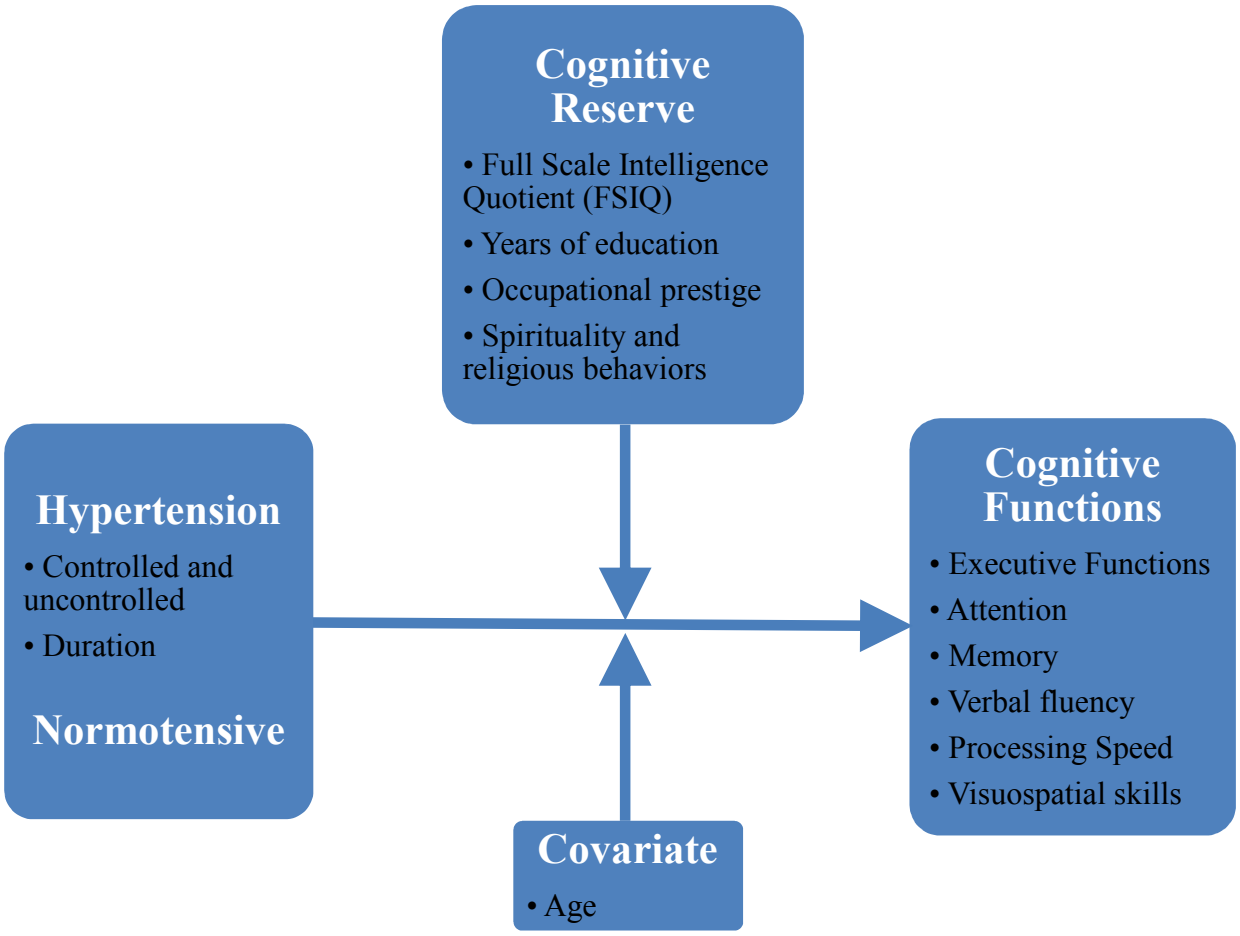


Figure 14: Conceptual Model of the Study

The present study had some limitations which can be improved by future research. A longitudinal experimental study is needed to infer a causal relationship between CR and cognitive function. This investigation could have had more precise measures of confounding variables related to clinical hypertension. In addition, this study was designed before the publication of JNC-8 recommendations and guidelines for hypertension (2014). The sample of this study wasa sample of convenience, which limits the generalizability of findings. The participants were volunteers, and there was not wide range of diversity in terms of race, religion, and occupation. Further, many of the volunteers were priests and nuns. This study utilized some

self-report measures that may be affected by forgetfulness and social desirability bias. In this sense, future research could take into account these limitations by studying the construct of brain reserve capacity with the help of neuroimaging. Researchers could also study the neuroprotection effect of CR against poor performance in cognitive functions by using the JNC-8 recommendations and stronger research designs (e.g., experimental or longitudinal).

Despite the limitations of this study, it is important to note here that the findings are valuable contributions to the literature on CR and hypertension. The current findings could be used as preliminary tools in the clinical assessment of high CR individuals with clinical hypertension. Our findings support the science underlining the importance of brain workouts in the protection against cognitive decline in normal aging and in individuals with neuropathology. This support of brain fitness is preliminarily evidenced by our finding an effect of CR even in older individuals with longer duration of disease.

APPENDIX A

I. Demographic Information
(To be filled by the participant)

Participant number:

Instructions: Please read and respond to all questions below by circling the appropriate choice:

1. Age (in years):

2. Gender:

a. Male
b. Female

3. Ethnicity

a. American Indian
b. Asian
c. Hispanic
d. Black/African American
e. Native Hawaiian/Pacific Islander
f. White
g. Two or more races
h. Other

4. Status:

a. Consecrated (religious order/diocese)
b. Lay person

5. Religious affiliation

a. Christian
b. Muslim
c. Hindu
d. Buddhist
e. No religion

6. Please circle the option below that best reflects your highest level of education. If no one of the options applies to you, then write your response in the space provided:

a. Completed elementary school (8 years)
b. Middle/Junior high (9-11 years)
c. Completed high school (12 years)

d. Completed technical education/Community college (12-13 years)
e. Completed college/university undergraduate degree (14-16 years)
f. Completed master program (17-18 years)
g. Completed graduate school (MD, PhD = more 19 years)

7. Years of education: _____

8. Please circle the option below that best reflects the area in which you received your highest level of education. If no one of the options applies to you, then write your response in the space provided:

a. Liberal arts
b. Fine arts
c. Science (Natural or Social)
d. Engineering
e. Law
f. Medicine/Health professions
g. Business
h. Education
i. Others: _____

9. List the different jobs and positions you have held in your life and their duration

a.
b.
c.
d.
e.
f.
g.
h.
i.
j.

10. Please circle the number of languages you speak:

a. One
b. Two
c. More than two

11. Please circle the category of your occupation

a. Semi-skilled, unskilled, skilled trade or craft, sales, agricultural/fishery, machine trades, benchwork, or structural occupation
b. Managerial, business or government, professional/teaching or technical

12. Please circle the option below which best reflects the salary you earned in your most recent full-time position or your occupation:

a. Less than $15,000 per year
b. $16,000 to $30, 000 per year
c. $30,001 to $80,000 per year
d. $80,001 to $100,000 per year
e. $100,001 to $250,000 per year
f. More than $250,001 per year

13. Please circle the option below which best reflects the amount of sleep you get on a typical night:
a. 0-4 hours
b. 5-6 hours
c. 7-8
d. More than 8 hours

14. Please circle the language spoken at home when you were a child

a. English
b. English and one other language
c. English and other languages

15. How many (a) full siblings do you have: _____
(b) Stepsiblings:_____
(c) Half-siblings: _____

16. Which of the statements on this list comes closest to describing your family situation **most the time** while you were growing up?

a. We were poor and had a hard time paying for food and housing.
b. We were poor but usually had had enough money to pay for food and housing
c. We had an adequate income for food and housing and were able to buy a few extras.
d. We had a pretty good income and were usually able to buy extras and special things.
e. We were well off or wealthy.

17. Please circle your parents' early socioeconomic status

a. Lower middle class (i.e., parents' level of education less than high school, income less than $4,000, and unskilled occupation).
b. Middle class (i.e., parents' level of education more than high school, income between $4,000-$10,000, and skilled managerial, professional, or technical occupation).
c. Upper middle class (i.e., parents' level of education college or more, income more than$10,000, and highly skilled managerial, professional, or technical occupation).
18. Please circle your father's level of education

a.Completed elementary school (8 years)

b.Middle/Junior high (9-11 years)
c.Completed high school (12 years)
d.Completed technical education/Community college (12-13 years)
e.Completed college/university undergraduate degree (14-16 years)
f.Completed master program (17-18 years)
g.Completed graduate school (MD, PhD = more 19 years)
h. Don't' Know (DK)

19. Please circle your mother or primary caregiver's level of education

a.Completed elementary school (8 years)
b.Middle/Junior high (9-11 years)
c.Completed high school (12 years)
d.Completed technical education/Community college (12-13 years)
e.Completed college/university undergraduate degree (14-16 years)
f.Completed master program (17-18 years)
g.Completed graduate school (MD, PhD = more 19 years)
h. Don't' Know (DK)

20. Please circle the option related to the quality of living accommodation during childhood and youth.

a. High quality
b. Average
c. Low quality
d. Don't Know (DK)

21. Please circle the option about your father's health

a. Had serious health problems
b. Did not have major health problems
c. Don't Know (DK)

22. Please circle the option about your mother or primary caregiver's health

a. Had serious health problems
b. Did not have major health problems
c. Don't Know (DK)

23. Please circle the option about your parent's encouragement of learning and for education

a. Strong
b. Adequate
c. Weak

d. Don't Know (DK)

24. If you have hypertension, please indicate probably which year and/or month was the onset of your hypertension:_____

25. If you have hypertension, please indicate your first level of blood pressure when you were first diagnosed with hypertension:_____

26. If you have hypertension, please indicate your first antihypertensive medication you were prescribed:_____
_____

27. If you have hypertension, please indicate in which year and month was your hypertension controlled (i.e., between 120/80 and 140/90)?_____

28. Please indicate how many years you have been in this nursing home or retirement house?
_____

II. Cognitive Reserve

Cognitive Activity Scale (CAS)

(Robert Wilson et al., 2003)

Participant number:

Please rate how often you participated in cognitive activities at age 6, age 12, age 18, age 40, and current age. Frequency of participation in each activity is on a 5-point scale: (5) every day or about every day; (4) several time a week; (3) several times a month; (2) several time a year; (1) once a year or less.

Reference age	**Items**	**Frequency**				
Age 6	Reading	1	2	3	4	5
	Playing games	1	2	3	4	5
	Telling stories	1	2	3	4	5
	Playing musical instrument	1	2	3	4	5
	Involvement with art	1	2	3	4	5
Age 12	Visiting library	1	2	3	4	5
	Reading newspapers	1	2	3	4	5
	Reading magazines	1	2	3	4	5
	Reading books	1	2	3	4	5
	Writing letters	1	2	3	4	5
	Playing games	1	2	3	4	5
	Playing musical instruments	1	2	3	4	5
	Involvement with art	1	2	3	4	5

Age 18	Visiting libraries	1	2	3	4	5
	Reading newspapers	1	2	3	4	5
	Reading magazines	1	2	3	4	5
	Reading books	1	2	3	4	5
	Writing letters	1	2	3	4	5
	Playing games	1	2	3	4	5
	Playing musical instrument	1	2	3	4	5
	Involvement with art	1	2	3	4	5
Age 40	Reading newspapers	1	2	3	4	5
	Reading magazines	1	2	3	4	5
	Reading books	1	2	3	4	5
	Writing letters	1	2	3	4	5
	Playing games	1	2	3	4	5
	Playing musical instrument	1	2	3	4	5
	Involvement with art	1	2	3	4	5
Present	Reading newspapers	1	2	3	4	5
	Reading magazines	1	2	3	4	5
	Reading books	1	2	3	4	5
	Writing letters	1	2	3	4	5
	Playing games	1	2	3	4	5

Playing musical instrument	1	2	3	4	5
Involvement with art	1	2	3	4	5

III. Physical Activity Questionnaire

Participant number:

Instructions: Please rate how often you participated in physical activities between ages 15-29, ages 30-49, ages 50-65, and your current age.

The questionnaire subdivides physical activities into 3 types: (a) Light exercise (e.g., bowling, leisurely walking, stretching, slow dancing, and golfing using a golf cart). (b) Moderate exercise: (e.g., brisk walking, hiking, aerobics, strength training, swimming, tennis doubles, yoga, martial arts, weight lifting, golfing without using a cart, and moderate use of an exercise machine like a bike). (c) Vigorous exercise: (e.g., jogging, backpacking, bicycling uphill, tennis singles, racquetball, skiing, and extended use of exercise machines).

2. Frequency of exercise Intensity

Instructions: Please circle the appropriate response for each age category whether you participate in none or any type of light, moderate or vigorous physical exercise at different ages.

Age	**Light**	**Moderate**	**Vigorous**
15-29	None or Any	None or Any	None or Any
30-49	None or Any	None or Any	None or Any
50-65	None or Any	None or Any	None or Any
After 65 or Present	None or Any	None or Any	None or Any

Frequency of Exercise

Instructions: Frequency of participation in each type of physical activity is on a 5-point scale: 0: None; (1): 2-3 month; (2): 1-2 times a week; (3): 3-4 times a week; (4): 5-6 times a week; (5): Daily.

Age **Type of exercise** **Frequency of Exercise**

15-29	Light	0	1	2	3	4	5
	Moderate	0	1	2	3	4	5
	Vigorous	0	1	2	3	4	5
30-49	Light	0	1	2	3	4	5
	Moderate	0	1	2	3	4	5
	Vigorous	0	1	2	3	4	5
50-65	Light	0	1	2	3	4	5
	Moderate	0	1	2	3	4	5
	Vigorous	0	1	2	3	4	5
After 65 or at Present	Light	0	1	2	3	4	5
	Moderate	0	1	2	3	4	5
	Vigorous	0	1	2	3	4	5

IV. Self-Report Questionnaire on Spirituality/Religiousness

Participant number:

1. Please indicate how often do you engage in private religious practice such as prayer, meditation, contemplation, etc.

0	1	2	3	4
Never	Once or twice a year	Every month	Every week	Daily

2. If you indicate "daily", please indicate how many times per day:

1	2	3
Once	Twice	Three or more times

3. On average, when you engage in private practice, how long do you do it? Please circle the response option that best fits you.

1	2	3	4
1-10 minutes	11-30 minutes	31-50 minutes	More than 50 minutes

4. How often do you engage in public religious activities such as attending or participating in formal religious services? Please circle the response option that best applies to you:

0	1	2	3	4
Never	At least once in the past year	At least once a month	At least once a weak	Daily

5. If you engage in public religious activities "daily", please indicate how many times per day by circling the best response option below:

1	2	3
Once	Twice	Three or more times

6. On average, for each social activity you participate in, how long do you do it?

1	2	3	4
1-10 minutes	11-30 minutes	31-50 minutes	More than 50 minutes

7. How often do you engage in social activities (e.g., non religious events) with members of your congregation or religion:

0	1	2	3	4
Never	At least once in the past year	At least once a month	At least once a weak	Daily

8. If you engage in social activities “daily”, please indicate how many times per day by circling the best response option below:

1	2	3
Once	Twice	Three or more times

9. On average, for each social activity you participate in, how long do you do it?

1	2	3	4
1-10 minutes	11-30 minutes	31-50 minutes	More than 50 minutes

10. Different people have different attitudes about whether or not religion and spirituality are the same. Please indicate to which of the following best represents your attitude about religion and spirituality

    a. Religion and spirituality are the same
    b. Religion and spirituality are not the same but related
    c. Religion and spirituality are different.

11. Referring to your answer to question 10, please indicate to what extend do you consider yourself as a spiritual person:

0	1	2	3
Not spiritual	Slightly spiritual	Moderately spiritual	Very spiritual

12. Referring to your answer to question 10, please indicate, to what extend do you consider yourself as a religious person

0	1	2	3
Not religious	Slightly religious	Moderately religious	Very religious

13. Using the rating scale provided, please rate the extent to which you feel that your spirituality or religiousness has benefited your physical health:

0	1	2	3
Not all	Somewhat	Moderate amount	A great deal

14. Using the rating scale provided, please rate the extent to which you feel that your spirituality or religiousness has benefited your mental health and emotional:

0	1	2	3
Not all	Somewhat	Moderate amount	A great deal

V. Medical Record Form

Medical Record Form

(To be filled by RN only)

Instructions: Please read and respond to all applicable questions below concerning this participant.

Participant number:
Year of birth:
Age:
Gender:

3. Please provide the results of the followings tests for within the past year, if available. Please use A for actual, MR from Medical Record.

Tests	**Results**	**Date**	**A**	**MR**
1. Height (cm)				
2. Weight (kg)				
3. Waist (cm)				
4. Blood pressure (BP)	BP (1st day) BP (2nd day) BP (3rd day)			
5. EKG doc HR				
6. BMI				
7. Blood glucose				
8. CBC				
9. Hematocrit				
10. Urinalysis				
11. Creatinine				

Tests	Results	Date	A	MR
Sodium				
Potassium				
15. Calcium				
16. Magnesium				
17. Chloride				
18. Hydrogen Phosphate				
19. Hydrogen carbonate				
20. Serum potassium				
21. Lipid				
22. High density lipoprotein cholesterol				
23. Low density lipoprotein cholesterol				
24. Triglycerides				
25. Thyroid				

5. Please list all the documented medical diagnoses of this participant and their date of onset in month and year. Please indicate whether this disease is Resolved (R), Current (C) or Chronic (Ch).

Medical Diagnosis	Date of Onset (Month/ Year)	R (Resolved)	C (Current)	Ch (Chronic)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

c. Please list all the documented psychiatric diagnoses of this participant, their dates of onset by providing the month and the year. Please indicate whether this disease is Resolved (R), Current (C) or Chronic (Ch).

Psychiatric Diagnosis	Date of Onset (Month/Year)	R (Resolved)	C (Current)	Ch (Chronic)
1				
2				
3				
4				
5				

4. Please list all the documented and non-documented medications of this participant (name, dose, frequency, and route).

Name of Medication	Dose	Frequency	Route	Rx (Prescribed) OTC (Over The Counter)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				

6. Please answer to each question for this participant either as Y for Yes, N for No or NS for Not Sure.

	Y	N	NS
1. Has this participant ever been treated with chemotherapy?			
2. Has this participant ever been treated with radiation?			
3. Has this participant ever been treated with hormone therapy?			
4. Has this participant ever undergone cardiac transplantation?			
5. Has this participant ever undergone carotid endarterectomy?			
6. Does this participant have metabolic syndrome (DM, HTN, and hypercholesterolemia)?			
7. Has this participant ever been involved in lifestyle modification and Dietary Approaches to Stop Hypertension (DASH)?			
8. Has this participant ever been involved in one of these diets (e.g., grains, vegetables, fruits, low fat or fat free dairy food, poultry and fish, nuts, seeds, and dry beans)?			
9. Has this participant ever been involved in avoidance of tobacco?			
10. Has this participant ever been involved in weight reduction?			
f. Has this participant ever been involved in dietary sodium reduction?			
12. Has this participant ever been involved in potassium, or calcium, or magnesium supplementation?			
13. Has this participant ever been involved in increased physical activity?			
14. Has this participant ever been involved in moderation of alcohol?			
15. Has this participant ever been involved in lipid-lowering diet and drug, protein intake, antioxidants, and caffeine?			
16. Is this participant aware of his/her hypertension?			

	Y	N	NS
17. Is this participant taking any antihypertensive medication?			
18. Is this participant hypertension controlled (i.e., <140/90)?			
19. Has one of this participant's parents had hypertension?			
20. Has one of this participant's siblings had hypertension?			

6. Please indicate all antihypertensive medications this participant is taking (dose, frequency, and route

Antihypertensive	Dose	Frequency	Route
1.			
2.			
3.			
4.			
5.			

7. Please circle by Y (Yes) or N (No) the option which reflects this participant's habits and hobbies

Habits or Hobbies	Past	Present
1. Alcohol		
2. Recovering alcoholic		
3. Tobacco		
4. Caffeinated drinks		
5. Amphetamine		
6. Marijuana		
7. Cocaine		

Habits or Hobbies	Past	Present
8. Opiates		
10. Ketamine		

8. Please provide the medical history of this participant's family as far as possible

	L (Living) or D (Died)	Age	Medical/Psychiatric diagnoses	Cause of death
Mother				
Father				

	L (Living) or D (Died)	Age	Medical/Psychiatric diagnoses	Cause of death
Siblings				

IV. Occupational Prestige Classification, Mini- Mental Status Exams (MMSE), and Health Literacy

APPENDIX F:

OCCUPATIONAL CLASSIFICATION DISTRIBUTIONS

(OCC, PRESTIGE, WRKSLF, WRKGOVT, COMMUTE, INDUSTRY, OCC80, PRESTG80, INDUS80, OCC10, INDUS10, SPOCC, SPWRKSLF, SPIND, SPOCC80, SPPRES80, SPOCC10, SPIND10, PAOCC16, PAPRES16, PAWRKSLF, PAIND16, PAOCC80, PAPRES80, PAIND80, PAOCC10, PAIND10, MAOCC80, MAPRES80, MAWRKSLF, MAIND80, MAOCC10, MAIND10)

This appendix contains three five-digit occupational classifications. In the first classification, the first three digits are the 1970 U.S. Census occupational codes, and the last two digits are the Hodge-Siegel-Rossi Prestige Scores. In the second classification the first three digits are the 1980 U.S. Census occupational codes and the last two digits are the NORC/GSS prestige scores. The third uses 2010 U.S. Census occupational codes.

The U.S. Census Bureau has assigned a three-digit number code to each occupational title. A listing of codes pertinent to this study was taken from an index of approximately 23,000 occupational titles. These codes appear under the column headed "Punch, Occupation." For further detail, see U.S. Bureau of the Census, 1970 Census of Population, Alphabetical Index of Industries and Occupations, Washington, U.S. Government Printing Office, 1971; U.S. Bureau of the Census, 1970 Census of Population, Classified Index of Industries and Occupations, Washington, U.S. Government Printing Office, 1971.; 1980 Census of Population, Alphabetical Index of Industries and Occupations, Washington, U.S. Government Printing Office, 1981; and U.S. Bureau of the Census, 1980 Census of Population, Classified Index of Industries and Occupations, Washington, U.S. Government Printing Office, 1981.

The frequencies for each occupational classification are listed in this appendix for the respondent, the respondent's father, the respondent's spouse, and the respondent's mother.

1970 Occupational Classification PROFESSIONAL, TECHNICAL, AND KINDRED WORKERS	Punch		N		
	Occupation	Prestige Scores	Respondent	R's Father	R's Spouse
PROFESSIONAL AND SPECIALTY					
Accountants	001	57	228	175	159
Architects	002	71	29	26	13
Computer specialists					
Computer programmers	003	51*	73	13	38
Computer systems analysts	004	51*	50	13	32
Computer specialists, n.e.c.	005	51*	30	8	25
Engineers					
Aeronautical astronautical engineers	006	71	7	35	8
Chemical engineers	010	67	18	27	18
Civil engineers	011	68	49	80	36
Electrical and electronic engineers	012	69	63	105	52
Industrial engineers	013	54	43	40	33
Mechanical engineers	014	62	43	90	33
Metallurgical and materials engineers	015	56	5	6	0
Mining engineers	020	62	2	9	3
Petroleum engineers	021	67	6	4	1
Sales engineers	022	51	2	3	8
Engineers, n.e.c.	023	67	36	33	25
Farm management advisers	024	54	7	3	5
Foresters and conservationists	025	54	18	15	9
Home management advisers	026	54*	2	0	0
Lawyers and judges					
Judges	030	76*	7	8	3
Lawyers	031	76	94	94	71
Librarians, archivists, and curators					
Librarians	032	55	42	0	30
Archivists and curators	033	66	4	0	1
Mathematical specialists					
Actuaries	034	55*	1	2	1
Mathematicians	035	65	1	1	2
Statisticians	036	55	4	3	3
Life and Physical scientists					
Agricultural scientists	042	56	5	6	4
Atmospheric and space scientists	043	68*	2	1	0
Biological scientists	044	68	15	3	11
Chemists	045	69	33	45	24
Geologists	051	67	11	3	4
Marine scientists	052	68*	0	0	0
Physicists and astronomers	053	74	2	5	6
Life and Physical scientists, n.e.c.	054	68	1	1	2
Operations and systems researchers and analysts	055	51	10	4	6
Personnel and labor relations workers	056	56	74	28	52
Physicians, dentists, and related practitioners					
Chiropractors	061	60	7	9	7
Dentists	062	74	27	40	14
Optometrists	063	62	7	8	6
Pharmacists	064	61	23	37	19

Health Diagnosing Practitioners, n.e.c.	089	50	15	10	9	1
Registered Nurses	095	66	588	17	297	705
Pharmacists	096	68	35	43	20	14
Dietitians	097	56	26	2	15	35
Inhalation Therapists	098	63	16	5	10	3
Occupational Therapists	099	56	16	0	10	5
Physical Therapists	103	61	31	1	22	13
Speech Therapists	104	61	29	0	12	10
Therapists, n.e.c.	105	62	30	1	11	6
Physicians' Assistants	106	61	15	6	7	7
Earth, Environmental, and Marine Science Teachers	113	74	6	2	0	1
Biological Science Teachers	114	74	6	7	3	2
Chemistry Teachers	115	74	4	5	1	3
Physics Teachers	116	74	3	3	1	0
Natural Science Teachers, n.e.c.	117	74	2	0	2	0
Psychology Teachers	118	74	8	3	2	1
Economics Teachers	119	74	6	9	3	1
History Teachers	123	74	7	3	4	3
Political Science Teachers	124	74	5	2	3	0
Sociology Teachers	125	74	0	2	0	1
Social Science Teachers, n.e.c.	126	74	2	1	1	1
Engineering Teachers	127	74	7	11	2	1
Mathematical Science Teachers	128	74	19	12	5	3
Computer Science Teachers	129	74	4	2	4	0
Medical Science Teachers	133	74	3	5	5	0
Health Specialties Teachers	134	74	11	1	10	4
Business, Commerce, and Marketing Teachers	135	74	5	11	5	1
Agriculture and Forestry Teachers	136	74	2	6	1	0
Art, Drama, and Music Teachers	137	74	22	9	11	6
Physical Education Teachers	138	74	2	2	4	1
Education Teachers	139	74	4	1	6	2
English Teachers	143	74	31	5	10	9
Foreign Language Teachers	144	74	17	3	3	1
Law Teachers	145	74	4	3	2	0
Social Work Teachers	146	74	3	0	0	0
Theology Teachers	147	74	3	6	3	0
Trade and Industrial Teachers	148	74	5	2	3	0
Home Economics Teachers	149	74	2	0	1	0
Teachers, Postsecondary, n.e.c.	153	74	6	10	5	2
Postsecondary Teachers, Subject Not Specified	154	74	64	38	30	15
Teachers, Prekindergarten and Kindergarten	155	55	110	1	58	79
Teachers, Elementary School	156	64	695	129	382	624
Teachers, Secondary School	157	66	361	185	177	227
Teachers, Special Education	158	65	49	2	17	28
Teachers, n.e.c.	159	46	183	41	83	66
Counselors, Educational and Vocational	163	57	80	14	38	21
Librarians	164	54	62	2	33	55
Archivists and Curators	165	52	11	2	4	2
Economists	166	63	62	19	23	7
Psychologists	167	69	66	17	24	9
Sociologists	168	61	1	0	0	0
Social Scientists, n.e.c.	169	65	8	5	4	3
Urban Planners	173	52	11	2	2	1
Social Workers	174	52	276	43	107	100
Recreation Workers	175	38	20	0	5	10
Clergy	176	69	81	197	56	2
Religious Workers, n.e.c.	177	44	21	5	10	9
Lawyers	178	75	176	168	115	12
Judges	179	71	5	10	2	5
Authors	183	63	33	3	10	1
Technical Writers	184	54	25	6	3	2
Designers	185	47	159	47	51	56
Musicians and Composers	186	47	56	25	23	16
Actors and Directors	187	58	47	7	19	4
Painters, Sculptors, Craft-Artists, and Printmakers	188	52	83	21	33	28
Photographers	189	45	36	24	21	4
Dancers	193	53	11	0	4	0
Artists, Performers, and Related Workers, n.e.c.	194	36	25	12	11	5
Editors and Reporters	195	60	83	23	33	35
Public Relations Specialists	197	48	56	17	20	7
Announcers	198	55	10	3	6	2

1980 Census Occupational Category	Punch 1980 Census Code	Punch 1989 Prestige Scores	N Respondent	N R's Father	N R's Spouse	N R's Mother
MANAGERIAL AND PROFESSIONAL SPECIALTY OCCUPATIONS						
Executive, Administrative, and Managerial Occupations						
Legislators	003	61	4	9	3	1
Chief Executives and General Admin., Public Admin.	004	70	5	15	2	1
Administrators and Officials, Public Administration	005	51	151	147	89	39
Administrators, Protective Service	006	54	13	19	10	0
Financial Managers	007	59	131	67	83	38
Personnel and Labor Relations Managers	008	54	34	19	21	15
Purchasing Managers	009	63	26	17	18	3
Managers, Marketing, Advertising, and Public Relations	013	59	171	112	95	18
Administrators, Education and Related Fields	014	64	188	145	106	40
Managers, Medicine and Health	015	69	126	22	59	38
Managers, Properties and Real Estate	016	39	115	49	65	26
Postmasters and Mail Superintendents	017	53	9	28	6	12
Funeral Directors	018	49	13	22	5	5
Managers and Administrators, n.e.c.	019	51	1939	1881	1156	461
Accountants and Auditors	023	65	351	265	173	142
Underwriters	024	48	6	2	1	4
Other Financial Officers	025	48	186	51	88	53
Management Analysts	026	61	110	11	31	5
Personnel, Training, and Labor Relations Specialists	027	43	124	43	90	37
Purchasing Agents and Buyers, Farm Products	028	42	5	19	5	1
Buyers, Wholesale and Retail Trade Except Farm Products	029	50	38	19	20	14
Purchasing Agents and Buyers	033	41	67	55	30	8
Business and Promotion Agents	034	51	16	4	5	4
Construction Inspectors	035	47	14	18	8	0
Inspectors/Compliance Officers, Except Construction	036	50	64	79	45	7
Management Related Occupations, n.e.c.	037	49	190	14	55	55
Professional Specialty Occupations						
Architects	043	73	42	45	23	7
Aerospace Engineers	044	72	28	71	21	1
Metallurgical and Materials Engineers	045	61	4	14	3	0
Mining Engineers	046	60	3	8	3	0
Petroleum Engineers	047	66	6	13	1	0
Chemical Engineers	048	73	19	54	10	3
Nuclear Engineers	049	63	1	6	7	0
Civil Engineers	053	69	68	161	46	4
Agricultural Engineers	054	60	0	1	0	0
Electrical and Electronic Engineers	055	64	113	212	94	7
Industrial Engineers	056	62	58	35	40	2
Mechanical Engineers	057	64	76	164	47	2
Marine and Naval Architects	058	59	1	6	2	0
Engineers, n.e.c.	059	71	87	85	38	0
Surveyors and Mapping Scientists	063	51	10	17	11	1
Computer Systems Analysts and Scientists	064	74	265	59	135	16
Operations and Systems Researchers and Analysts	065	53	14	4	11	1
Actuaries	066	44	2	0	2	0
Statisticians	067	56	8	3	4	0
Mathematical Scientists, n.e.c.	068	63	2	3	2	1
Physicists and Astronomers	069	73	4	14	4	1
Chemists, Except Biochemists	073	73	31	60	24	7
Atmospheric and Space Scientists	074	63	4	6	1	0
Geologists and Geodesists	075	70	8	7	7	1
Physical Scientists, n.e.c.	076	73	9	5	7	0
Agricultural and Food Scientists	077	58	11	12	7	3
Biological and Life Scientists	078	73	26	2	10	9
Forestry and Conservation Scientists	079	55	7	16	8	0
Medical Scientists	083	64	9	3	9	5
Physicians	084	86	115	179	91	25
Dentists	085	72	28	51	20	6
Veterinarians	086	62	11	21	11	3
Optometrists	087	67	7	10	8	2
Podiatrists	088	65	3	3	1	0

Athletes	199	65	32	4	7	0
TECHNICAL, SALES, AND ADMINISTRATIVE SUPPORT OCCUPATIONS						
Technicians and Related Support Occupations						
Clinical Laboratory Technologists and Technicians	203	68	99	8	43	30
Dental Hygienists	204	52	22	0	15	19
Health Record Technologists and Technicians	205	52	11	0	7	5
Radiologic Technicians	206	58	37	10	21	11
Licensed Practical Nurses	207	60	150	6	69	147
Health Technologists and Technicians, n.e.c.	208	57	118	6	46	28
Electrical and Electronic Technicians	213	60	144	51	77	9
Industrial Engineering Technicians	214	40	3	5	0	0
Mechanical Engineering Technicians	215	54	4	1	0	0
Engineering Technicians, n.e.c.	216	48	52	24	25	3
Drafting Occupations	217	51	60	60	19	6
Surveying and Mapping Technicians	218	36	9	11	4	0
Biological Technicians	223	32	18	7	8	4
Chemical Technicians	224	38	37	18	15	3
Science Technicians, n.e.c.	225	44	31	15	21	4
Airplane Pilots and Navigators	226	61	37	65	24	0
Air Traffic Controllers	227	65	12	12	3	1
Broadcast Equipment Operators	228	43	21	15	8	5
Computer Programmers	229	61	145	61	74	28
Tool Programmers, Numerical Control	233	48	2	1	1	0
Legal Assistants	234	57	82	3	29	30
Technicians, n.e.c.	235	41	121	48	44	14
Sales Occupations						
Supervisors and Proprietors, Sales Occupations	243	44	713	841	406	259
Insurance Sales Occupations	253	45	160	215	86	43
Real Estate Sales Occupations	254	49	218	98	106	104
Securities and Financial Services Sales Occupations	255	53	86	31	43	5
Advertising and Related Sales Occupations	256	39	42	15	24	4
Sales Occupations, Other Business Services	257	32	87	34	51	15
Sales Engineers	258	53	8	3	4	0
Sales Rep., Mining, Manufacturing, and Wholesale	259	49	285	364	164	37
Sales Workers, Motor Vehicles and Boats	263	34	60	115	31	6
Sales Workers, Apparel	264	30	126	20	52	125
Sales Workers, Shoes	265	28	19	9	13	13
Sales Workers, Furniture and Home Furnishings	266	31	42	28	24	18
Sales Workers, Radio, TV, Hi-Fi, and Appliances	267	31	38	27	18	9
Sales Workers, Hardware and Building Supplies	268	32	40	33	22	7
Sales Workers, Parts	269	30	32	27	15	3
Sales Workers, Other Commodities	274	32	513	159	214	419
Sales Counter Clerks	275	34	50	16	17	22
Cashiers	276	29	648	16	192	348
Street and Door-To-Door Sales Workers	277	22	98	30	34	58
News Vendors	278	19	16	9	7	8
Demonstrators, Promoters and Models, Sales	283	32	18	0	5	5
Auctioneers	284	39	0	0	0	0
Sales Support Occupations, n.e.c.	285	36	12	4	8	0
Administrative Support Occupations, Including Clerical						
Supervisors, General Office	303	51	145	25	62	50
Supervisors, Computer Equipment Operators	304	54	14	6	2	2
Supervisors, Financial Records Processing	305	52	19	12	11	10
Chief Communications Operators	306	49	5	7	8	4
Supervisors, Distribution, Scheduling, and Adjusting Clerks	307	42	48	50	29	8
Computer Operators	308	50	66	13	34	13
Peripheral Equipment Operators	309	40	4	0	4	1
Secretaries	313	46	968	14	490	1084
Stenographers	314	47	25	4	15	17
Typists	315	40	66	1	30	31
Interviewers	316	49	30	4	14	9
Hotel Clerks	317	32	31	0	10	8
Transportation Ticket and Reservation Agents	318	35	34	12	22	15
Receptionists	319	39	231	6	122	95
Information Clerks, n.e.c.	323	34	13	0	5	0
Classified-Ad Clerks	325	31	3	0	2	2
Correspondence Clerks	326	35	3	0	1	1

Order Clerks	327	31	92	8	27	26
Personnel Clerks, Except Payroll and Timekeeping	328	36	20	7	6	15
Library Clerks	329	29	48	3	14	14
File Clerks	335	36	27	2	10	13
Records Clerks	336	31	44	4	25	14
Bookkeepers, Accounting and Auditing Clerks	337	47	424	55	231	352
Payroll and Timekeeping Clerks	338	42	47	10	16	33
Billing Clerks	339	31	72	1	35	13
Cost and Rate Clerks	343	28	11	4	7	2
Billing, Posting, and Calculating Machine Operators	344	35	27	0	12	3
Duplicating Machine Operators	345	35	3	0	3	2
Mail Preparing and Paper Handling Machine Operators	346	36	2	0	0	0
Office Machine Operators, n.e.c.	347	39	8	0	3	1
Telephone Operators	348	40	91	4	26	103
Telegraphers	349	45	1	6	1	1
Communications Equipment Operators, n.e.c.	353	33	2	2	1	1
Postal Clerks, Excluding Mail Carriers	354	42	89	67	35	52
Mail Carriers, Postal Service	355	47	77	159	45	23
Mail Clerks, Excluding Postal Service	356	32	44	12	14	10
Messengers	357	22	35	6	14	0
Dispatchers	359	35	37	23	29	11
Production Coordinators	363	42	49	11	27	7
Traffic, Shipping and Receiving Clerks	364	33	158	59	69	31
Stock and Inventory Clerks	365	27	132	46	59	27
Meter Readers	366	34	11	19	7	0
Weighers, Measurers, and Checkers	368	28	15	9	5	4
Samplers	369	35	1	0	0	0
Expediters	373	43	73	13	25	17
Material Recording, Scheduling and Distributing Clerks, n.e.c.	374	24	7	2	3	4
Insurance Adjusters, Examiners, and Investigators	375	47	87	18	30	19
Investigators and Adjusters, Except Insurance	376	40	201	14	73	46
Eligibility Clerks, Social Welfare	377	46	11	0	9	3
Bill and Account Collectors	378	24	33	5	16	11
General Office Clerks	379	34	414	58	162	223
Bank Tellers	383	43	111	8	58	101
Proofreaders	384	43	6	1	1	10
Data-Entry Keyers	385	41	121	6	40	43
Statistical Clerks	386	38	14	1	5	5
Teachers' Aides	387	43	106	1	54	88
Administrative Support Occupations, n.e.c.	389	33	212	21	96	63
SERVICE OCCUPATIONS						
Private Household Occupations						
Launderers and Ironers	403	23	4	1	1	33
Cooks, Private Household	404	30	13	2	7	19
Housekeepers and Butlers	405	34	29	1	9	58
Child Care Workers, Private Household	406	29	127	1	42	61
Private Household Cleaners and Servants	407	23	242	8	66	510
Protective Service Occupations						
Supervisors, Firefighting and Fire Prevention Occupations	413	60	7	6	4	0
Supervisors, Police and Detectives	414	62	20	21	7	1
Supervisors, Guards	415	38	18	6	9	0
Fire Inspection and Fire Prevention Occupations	416	60	8	11	5	0
Firefighting Occupations	417	53	56	108	28	1
Police and Detectives, Public Service	418	60	144	198	78	21
Sheriffs, Bailiffs, and Other Law Enforcement Officers	423	48	36	25	21	2
Correctional Institution Officers	424	40	56	31	42	3
Crossing Guards	425	32	16	0	8	11
Guards and Police, Excluding Public Service	426	42	140	109	62	35
Protective Service Occupations	427	37	14	2	7	1
Armed Forces[1]						
Former Member of the Armed Forces	430	49	48	92	29	0
Current Member of the Armed Forces	431	49	114	328	93	20
Service Occupations, Except Protective and Household						
Supervisors, Food Preparation and Service Occupations	433	35	100	24	45	40
Bartenders	434	25	97	28	26	36

[1]These codes are not part of the 1980 Census Occupational Classification. They are codes used by NORC.

Waiters and Waitresses	435	28	466	25	113	451
Cooks, Except Short Order	436	31	377	96	131	419
Short-Order Cooks	437	28	15	3	3	6
Food Counter, Fountain and Related Occupations	438	23	49	1	8	10
Kitchen Workers, Food Preparation	439	24	78	8	20	29
Waiters'/Waitresses' Assistants	443	21	86	7	28	32
Miscellaneous Food Preparation Occupations	444	17	160	11	42	148
Dental Assistants	445	45	49	0	33	36
Health Aids, Except Nursing	446	51	188	6	60	50
Nursing Aides, Orderlies and Attendants	447	42	625	15	184	460
Supervisors, Cleaning and Building Service Workers	448	36	57	31	25	15
Maids and Housemen	449	20	198	13	66	207
Janitors and Cleaners	453	22	532	320	221	211
Elevator Operators	454	28	1	5	2	4
Pest Control Occupations	455	32	13	14	9	0
Supervisors, Personal Service Occupations	456	37	14	6	4	7
Barbers	457	36	18	66	11	4
Hairdressers and Cosmetologists	458	36	241	15	101	199
Attendants, Amusement and Recreation Facilities	459	25	46	10	17	10
Guides	463	29	6	0	7	0
Ushers	464	20	2	0	0	3
Public Transportation Attendants	465	42	19	7	11	8
Baggage Porters and Bellhops	466	27	6	9	4	1
Welfare Service Aides	467	46	65	3	16	26
Child Care Workers, Except Private Household	468	36	269	2	122	177
Personal Service Occupations, n.e.c.	469	25	66	6	24	28
FARMING, FOREST, AND FISHING OCCUPATIONS						
Farm Operators and Managers						
Farmers, Except Horticultural	473	40	223	2844	144	91
Horticultural Specialty Farmers	474	37	16	21	5	0
Managers, Farms, Except Horticultural	475	48	17	59	6	1
Managers, Horticultural Specialty Farms	476	48	10	23	5	1
Farm Occupations, Except Managerial						
Supervisors, Farm Workers	477	44	6	22	2	2
Farm Workers	479	23	146	452	43	140
Marine Life Cultivation Workers	483	31	31	0	1	0
Nursery Workers	484	26	11	6	0	9
Related Agricultural Occupations						
Supervisors, Related Agricultural Occupations	485	36	22	21	10	1
Groundskeepers and Gardeners, Except Farm	486	29	129	122	75	4
Animal Caretakers, Except Farm	487	21	29	10	11	6
Graders and Sorters, Agricultural Products	488	31	7	1	0	3
Inspectors, Agricultural Products	489	49	2	0	1	0
Forestry and Logging Occupations						
Supervisors, Forestry and Logging Workers	494	44	1	11	1	0
Forestry Workers, Except Logging	495	39	7	6	3	1
Timber Cutting and Logging Occupations	496	31	19	107	14	1
Fishers, Hunters, and Trappers						
Captains and Other Officers, Fishing Vessels	497	43	1	2	3	0
Fishers	498	34	19	60	4	1
Hunters and Trappers	499	23	23	2	1	0
PRECISION PRODUCTION, CRAFT, AND REPAIR OCCUPATIONS						
Mechanics and Repairers						
Supervisors, Mechanics and Repairers	503	50	54	74	40	2
Automobile Mechanics, Except Apprentices	505	40	206	405	126	4
Automobile Mechanic Apprentices	506	34	34	1	0	0
Bus, Truck, and Stationary Engine Mechanics	507	44	73	123	38	1
Aircraft Engine Mechanics	508	53	29	38	20	1
Small Engine Repairers	509	28	13	18	4	0
Automobile Body and Related Repairers	514	31	60	68	23	1
Aircraft Mechanics, Excluding Engine	515	53	19	16	12	0

Heavy Equipment Mechanics	516	45	42	80	27	0
Farm Equipment Mechanics	517	36	5	25	3	0
Industrial Machinery Repairers	518	30	69	168	36	5
Machinery Maintenance Occupations	519	26	5	13	1	0
Electronic Repairers, Communications and Industrial Equipment	523	39	51	49	14	1
Data Processing Equipment Repairers	525	51	20	14	17	0
Household Appliance and Power Tool Repairers	526	38	23	30	11	0
Telephone Line Installers and Repairers	527	41	29	47	9	0
Telephone Installers and Repairers	529	36	30	56	24	4
Misc. Electrical and Electronic Equipment Repairers	533	39	17	18	5	0
Heating, Air Conditioning, and Refrigeration Mechanics	534	42	73	54	33	0
Camera, Watch, and Musical Instrument Repairers	535	35	6	17	8	2
Locksmiths and Safe Repairers	536	39	10	5	5	0
Office Machine Repairers	538	37	9	7	8	0
Mechanical Controls and Valve Repairers	539	36	5	3	3	0
Elevator Installers and Repairers	543	39	5	12	5	0
Millwrights	544	43	19	50	19	1
Specified Mechanics and Repairers, n.e.c.	547	32	46	60	28	1
Not Specified Mechanics and Repairers	549	44	38	58	26	1
Construction Trades						
Supervisors, Brickmasons, Stonemasons, and Title Setters	553	50	2	6	1	0
Supervisors, Carpenters and Related Work	554	50	5	4	7	0
Supervisors, Electricians and Power Transmission Installers	555	50	13	19	8	0
Supervisors, Painters, Paperhangers, and Plasterers	556	50	4	7	2	0
Supervisors, Plumbers, Pipefitters, and Steamfitters	557	50	6	11	5	0
Supervisors, n.e.c.	558	54	143	276	111	0
Brickmasons and Stonemasons, Except Apprentices	563	36	48	132	24	1
Brickmasons and Stonemasons Apprentices	564	26	26	1	3	0
Tile Setters, Hard and Soft	565	31	16	17	7	0
Carpet Installers	566	34	16	25	10	0
Carpenters, Except Apprentices	567	39	320	594	151	1
Carpenter Apprentices	569	29	29	1	0	0
Drywall Installers	573	34	28	27	6	0
Electricians, Except Apprentices	575	51	158	313	116	5
Electrician Apprentices	576	41	9	2	5	0
Electrical Power Installers and Repairers	577	46	25	41	19	0
Painters, Construction and Maintenance	579	34	94	166	51	3
Paperhangers	583	31	7	8	2	3
Plasterers	584	35	6	24	4	0
Plumbers, Pipefitters, and Steamfitters, Except Apprentices	585	45	134	224	80	0
Plumber, Pipefitter, and Steamfitter Apprentices	587	35	2	4	2	0
Concrete and Terrazzo Finishers	588	38	19	26	12	0
Glaziers	589	30	5	10	6	0
Insulation Workers	593	33	11	7	8	0
Paving, Surfacing, and Tamping Equipment Operators	594	33	2	1	4	1
Roofers	595	37	48	37	23	1
Sheetmetal Duct Installers	596	35	12	16	5	1
Structural Metal Workers	597	43	23	56	16	0
Drillers, Earth	598	40	4	13	4	0
Construction Trades, n.e.c.	599	36	40	68	19	0
Extractive Occupations						
Supervisors, Extractive Occupations	613	44	10	33	2	0
Drillers, Oil Well	614	42	5	23	5	0
Explosives Workers	615	38	2	8	0	0
Mining Machine Operators	616	35	14	211	5	2
Precision Production Occupations						
Mining Occupations, n.e.c.	617	29	9	49	3	0
Supervisors, Production Occupations	633	47	254	525	188	62
Tool and Die Makers, Except Apprentices	634	43	35	134	20	1
Tool and Die Maker Apprentices	635	33	33	0	0	0
Precision Assemblers, Metal	636	31	6	14	5	3
Machinists, Except Apprentices	637	47	106	317	73	6
Machinist Apprentices	639	35	1	0	0	0
Boilermakers	643	40	4	30	6	0
Precision Grinders, Fitters, and Tool Sharpeners	644	26	2	5	6	0
Patternmakers and Model Makers, Metal	645	38	1	5	2	0
Lay-Out Workers	646	30	30	3	0	0
Precious Stones and Metals Workers	647	45	13	10	9	3

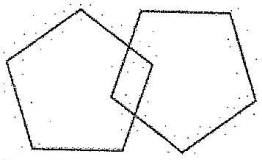
Engravers, Metal	649	38	1	3	1	0
Sheet Metal Workers, Except Apprentices	653	50	22	50	12	0
Sheet Metal Worker, Apprentices	654	38	1	0	0	0
Miscellaneous Precision Metal Workers	655	36	2	0	1	0
Patternmakers and Model Makers, Wood	656	39	39	2	1	0
Cabinet Makers and Bench Carpenters	657	44	24	25	16	5
Furniture and Wood Finishers	658	39	13	17	8	3
Miscellaneous Precision Woodworkers	659	36	2	3	0	0
Dressmakers	666	36	43	3	23	191
Tailors	667	42	15	42	5	20
Upholsterers	668	35	26	19	9	5
Shoe Repairers	669	36	10	36	1	5
Apparel and Fabric Patternmakers	673	37	2	1	2	0
Miscellaneous Precision Apparel and Fabric Workers	674	34	5	4	3	14
Hand Molders and Shapers, Except Jewelers	675	32	10	17	3	2
Patternmakers, Lay-Out Workers, and Cutters	676	28	6	6	3	1
Optical Goods Workers	677	38	21	13	8	5
Dental Laboratory and Medical Appliance Technicians	678	56	12	11	4	5
Bookbinders	679	32	12	7	4	10
Electrical and Electronic Equipment Assemblers	683	28	43	12	19	55
Miscellaneous Precision Workers, n.e.c.	684	30	8	9	2	2
Butchers and Meat Cutters	686	35	49	128	27	19
Bakers	687	35	46	53	23	29
Food Batchmakers	688	30	14	10	4	13
Inspectors, Testers, and Graders	689	42	32	38	21	12
Adjusters and Calibrators	693	40	4	2	1	0
Water and Sewage Treatment Plant Operators	694	38	13	10	10	0
Power Plant Operators	695	43	6	7	5	0
Stationary Engineers	696	40	29	68	13	1
Miscellaneous Plant and System Operators	699	43	8	21	12	1
OPERATORS, FABRICATORS, AND LABORERS						
Machine Operators, Assemblers, and Inspectors						
Lathe and Turning Machine Set-Up Operators	703	41	8	5	4	0
Lathe and Turning Machine Operators	704	37	11	19	7	2
Milling and Planing Machine Operators	705	32	2	4	1	0
Punching and Stamping Press Machine Operators	706	35	32	19	17	10
Rolling Machine Operators	707	40	1	10	1	0
Drilling and Boring Machine Operators	708	37	12	12	4	2
Grinding, Abrading, Buffing, and Polishing Machine Operators	709	23	28	26	16	3
Forging Machine Operators	713	36	3	8	0	0
Miscellaneous Metal, Plastic, Stone, and Glass Working Machine Operators	715	29	5	5	2	2
Fabricating Machine Operators, n.e.c.	717	38	7	4	7	12
Molding and Casting Machine Operators	719	34	36	41	21	11
Metal Plating Machine Operators	723	36	8	8	12	2
Heat Treating Equipment Operators	724	40	4	4	2	0
Miscellaneous Metal and Plastic Processing Machine Operators	725	35	3	2	3	0
Wood Lathe, Routing and Planing Machine Operators	726	37	4	3	1	1
Sawing Machine Operators	727	34	32	74	15	1
Shaping and Joining Machine Operators	728	30	1	0	1	1
Nailing and Tacking Machine Operators	729	27	2	0	0	1
Miscellaneous Woodworking Machine Operators	733	22	11	10	1	2
Printing Machine Operators	734	39	84	82	30	12
Photoengravers and Lithographers	735	40	11	10	5	1
Typesetters and Compositors	736	40	14	23	7	7
Miscellaneous Printing Machine Operators	737	37	16	2	8	5
Winding and Twisting Machine Operators	738	30	32	15	10	42
Knitting, Looping, Taping, and Weaving Machine Operators	739	34	19	21	6	40
Textile Cutting Machine Operators	743	28	7	0	3	310
Textile Sewing Machine Operators	744	28	210	23	83	410
Shoe Machine Operators	745	33	17	10	6	37
Pressing Machine Operators	747	29	32	10	13	35
Laundering and Dry Cleaning Machine Operators	748	32	73	35	13	88
Miscellaneous Textile Machine Operators	749	33	33	45	12	52
Cementing and Gluing Machine Operators	753	35	8	1	5	3
Packaging and Filling Machine Operators	754	25	47	20	19	75
Extruding and Forming Machine Operators	755	32	10	5	4	3
Mixing and Blending Machine Operators	756	26	20	32	15	5
Separating, Filtering, and Clarifying Machine Operators	757	30	14	30	11	4
Compressing and Compacting Machine Operators	758	30	2	4	0	1

Painting and Paint Spraying Machine Operators	759	30	38	35	16	5
Roasting and Baking Machine Operators, Food	763	23	1	1	0	0
Washing, Cleaning, and Pickling Machine Operators	764	25	2	2	1	1
Folding Machine Operators	765	28	4	0	2	7
Furnace, Kiln, and Oven Operators, Except Food	766	40	31	96	18	1
Crushing and Grinding Machine Operators	768	31	6	15	4	3
Slicing and Cutting Machine Operators	769	34	36	22	15	11
Motion Picture Projectionists	773	38	5	5	1	1
Photographic Process Machine Operators	774	38	22	1	7	10
Miscellaneous and Not Specified Machine Operators, n.e.c.	777	30	195	175	84	68
Machine Operators, Not Specified	779	33	176	375	96	197
Welders and Cutters	783	42	140	244	75	13
Solderers and Blazers	784	33	17	3	3	10
Assemblers	785	35	284	233	145	321
Hand Cutting and Trimming Occupations	786	26	5	1	2	5
Hand Molding, Casting, and Forming Occupations	787	33	8	6	4	8
Hand Painting,Coating, and Decorating Occupations	789	31	11	11	4	3
Hand Engraving and Printing Occupations	793	42	1	0	3	0
Hand Grinding and Polishing Occupations	794	35	35	1	0	0
Miscellaneous Hand Working Occupations	795	32	12	9	4	3
Production Inspectors, Checkers, and Examiners	796	36	175	87	82	73
Production Testers	797	38	16	10	6	3
Production Samplers and Weighers	798	42	1	0	0	18
Graders and Sorters, Except Agricultural	799	33	19	12	10	29
Transportation and Material Moving Occupations						
Supervisors, Motor Vehicle Operators	803	38	20	17	6	2
Truck Drivers, Heavy	804	30	485	863	305	7
Truck Drivers, Light	805	30	112	100	76	7
Driver-Sales Workers	806	24	38	98	32	4
Bus Drivers	808	32	128	80	63	75
Taxicab Drivers and Chauffeurs	809	28	57	87	25	9
Parking Lot Attendants	813	21	7	3	3	0
Motor Transportation Occupations, n.e.c.	814	25	3	3	1	0
Railroad Conductors and Yardmasters	823	42	15	86	8	0
Locomotive Operating Occupations	824	41	17	72	9	0
Railroad Brake, Signal, and Switch Operators	825	40	6	58	4	0
Rail Vehicle Operators, n.e.c.	826	47	47	6	1	0
Ship Captains and Mates, Except Fishing Boats	828	54	1	15	2	0
Sailors and Deckhands	829	34	4	19	5	0
Marine Engineers	833	43	43	0	1	0
Bridge, Lock and Lighthouse Tenders	834	28	28	1	1	0
Supervisors, Material Moving Equipment Operators	843	45	6	10	6	1
Operating Engineers	844	50	75	109	42	0
Longshore Equipment Operators	845	34	3	6	1	0
Hoist and Winch Operators	848	36	4	4	1	0
Crane and Tower Operators	849	42	20	64	17	1
Excavating and Loading Machine Operators	853	38	19	17	11	0
Grader, Dozer, and Scraper Operators	855	34	11	31	9	0
Industrial Truck and Tractor Equipment Operators	856	35	102	85	62	4
Miscellaneous Material Moving Equipment Operators	859	27	53	34	25	3
Handlers, Equipment Cleaners, Helpers, and Laborers, n.e.c.	863	27	6	6	3	0
Helpers, Mechanics and Repairers	864	33	2	1	1	0
Helpers, Construction Trades	865	30	10	4	4	1
Helpers, Surveyor	866	38	3	2	1	0
Helpers, Extractive Occupations	867	38	1	0	0	0
Construction Laborers	869	36	327	537	154	8
Production Helpers	873	31	8	4	6	1
Garbage Collectors	875	28	9	32	13	1
Stevedores	876	37	5	38	6	0
Stock Handlers and Baggers	877	23	120	31	50	48
Machine Feeders and Offbearers	878	37	16	5	4	8
Freight, Stock, and Material Handlers, n.e.c.	883	27	112	84	45	3
Garage and Service Station Related Occupations	885	21	30	29	8	3
Vehicle Washers and Equipment Cleaners	887	19	35	23	17	6
Hand Packers and Packagers	888	22	131	31	46	97
Laborers, Except Construction	889	24	300	645	161	213
Don't know	998	IAP	1	53	5	15
No answer	999	IAP	324	769	280	483
Not applicable (Unemployed, No father substitute, Not married, Disabled, Retired)	IAP	IAP	23,328	28,773	39,474	40,276

The Mini-Mental State Exam

Patient_____ Examiner _____ Date_____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

ASSESS level of consciousness along a continuum _____

Alert Drowsy Stupor Coma

Nutrition Facts

Serving Size	½ cup
Servings per container	4
Amount per serving	
Calories 250	Fat Cal 120
	%DV
Total Fat 13g	20%
Sat Fat 9g	40%
Cholesterol 28mg	12%
Sodium 55mg	2%
Total Carbohydrate 30g	12%
Dietary Fiber 2g	
Sugars 23g	
Protein 4g	8%

*Percentage Daily Values (DV) are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

Ingredients: Cream, Skim Milk, Liquid Sugar, Water, Egg Yolks, Brown Sugar, Milkfat, Peanut Oil, Sugar, Butter, Salt, Carrageenan, Vanilla Extract.

Score Sheet for the Newest Vital Sign Questions and Answers

READ TO SUBJECT: This information is on the back of a container of a pint of ice cream.

ANSWER CORRECT?	
yes	**no**

1. If you eat the entire container, how many calories will you eat?

   Answer: *1,000 is the only correct answer*

2. If you are allowed to eat 60 grams of carbohydrates as a snack, how much ice cream could you have?

   Answer: *Any of the following is correct: 1 cup (or any amount up to 1 cup), Half the container Note: If patient answers "two servings," ask "How much ice cream would that be if you were to measure it into a bowl."*

3. Your doctor advises you to reduce the amount of saturated fat in your diet. You usually have 42 g of saturated fat each day, which includes one serving of ice cream. If you stop eating ice cream, how many grams of saturated fat would you be consuming each day?

   Answer: *33 is the only correct answer*

4. If you usually eat 2500 calories in a day, what percentage of your daily value of calories will you be eating if you eat one serving?

   Answer: *10% is the only correct answer*

READ TO SUBJECT: Pretend that you are allergic to the following substances: Penicillin, peanuts, latex gloves, and bee stings.

5. Is it safe for you to eat this ice cream?

   Answer: *No*

6. (Ask only if the patient responds "no" to question 5): Why not?

   Answer: *Because it has peanut oil.*

Interpretation

Number of correct answers:

Score of 0-1 suggests high likelihood (50% or more) of limited literacy
Score of 2-3 indicates the possibility of limited literacy.
Score of 4-6 almost always indicates adequate literacy.

VI. Cognitive Measures

1. **Memory Tests**

Rey Complex Figure Test (RCFT): Cannot be attached due to copyright

Rey Auditory Verbal Learning Test: Cannot be attached due to copyright

2. **Attention Tests**

Wechsler Adult Scale of Intelligence- Fourth Edition (WAIS-IV): Digit Span (DS), Letter Numbering Sequencing (LNS): Cannot be attached due to copyright

Trail Making Test B: Cannot be attached due to copyright

3. **Processing Speed Tests**

Wechsler Adult Scale of Intelligence- Fourth Edition (WAIS-IV): Coding (CD): Cannot be attached due to copyright.

Trail Making Test A: Cannot be attached due to copyright

4. **Executive Functions**

D-KEFS Color-Word Interference Test: Cannot be attached due to copyright

D-KEFS Design Fluency Test: Cannot be attached due to copyright

5. **Verbal Fluency Tests**

Verbal Fluency Tests (FAS & Animals): Cannot be attached due to copyright.

6. **Visual Spatial Abilities**

Wechsler Adult Scale of Intelligence- Fourth Edition (WAIS-IV): Block Design (BS): Cannot be attached due to copyright.

7. **Measure of Full Scale Intellectual Quotient (FSIQ)**

Wechsler Abbreviated Scale of Intelligence- Second Edition: Vocabulary and Matrix Reasonning (WASI-II): Cannot be attached due to copyright.

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ABSTRACT

COGNITIVE RESERVE AS NEUROPROTECTION FOR COGNITIVE FUNCTIONS IN INDIVIDUALS WITH CLINICAL HYPERTENSION

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Clinical hypertension is associated with impaired neuropsychological functioning. While cognitive reserve (CR) delays neurocognitive decline, CR's neuroprotective effects on the association between clinical hypertension and cognitive function has not been studied intensively. This study examined CR's moderation impact with cognitive performance in 150 individuals normotensive and hypertensive recruited in Michigan and Illinois and evaluated whether this relationship is moderated by CR. Participants were assessed with a neuropsychological battery, WASI-II, completed self-report measures on their leisure activities, spiritual and religious behaviors, and health measures. A CR-factor, combining IQ, years of education, occupational prestige, and spiritual and religious behaviors, significantly revealed a moderation effect of CR on the association between clinical hypertension and cognitive function.

Participants with hypertension older than 72.5 years showed greater neuroprotection. These findings suggest a neuroprotective effect of CR against poor cognitive performance in individuals with clinical hypertension, particularly for older individuals with longer duration of the disease.

AUTOBIOGRAPHICAL STATEMENT

Born of farmer parents in the Democratic Republic of Congo, I learned that hard work pays off and that it takes patience, collaboration, and particular attention to nature to harvest good fruit. From a very young age, I understood that I was a child of my tribe, my ethnic group, and my village, all of whom contributed to my upbringing. I thus became aware that I was a small dot in the macro system that was my family, tribe, ethnic group, and ancestors; I learned the values of hospitality, solidarity, and service. My elementary and high school education instilled in me a passion for science, an openness to diversity, and a love of excellence. My dream for a better life, however, came to maturity in a country where a dictatorship silenced education and science, promoted oppression, and rewarded tribalism and nepotism.

In this context of civil war, violence, rape, poverty, disease, and short life expectancy, my Christian tradition sustained in me the hope for a better tomorrow, joy in time of suffering, and courage in the midst of despair. This Christian education led me to become a priest in a religious order where I learned to live with people from different cultures, races, languages, and countries. I learned to believe what I understand and to understand what I believe. My pastoral experiences with people during the most important stages of life (e.g., birth, marriage, and death) and circumstances (e.g., happiness, success, war, violence, and trauma) answered some of my existential questions and gave meaning to my future social and academic endeavors.

My ignorance and frustration in dealing with the enormity of these sufferings in my country explained my unquenchable thirst for different academic disciplines. Philosophy and theology prepared me to think epistemologically and hermeneutically about human existence and destiny, while psychology, neuroscience, and medicine have introduced me into thinking

critically and therapeutically about human questions. My life has been a balance between the altar and the lab, Bible and DSM, religion and science. Experience in these two arenas has given me the opportunity to meet humanity in its complexity and diverse aspects.