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Subclinical Vascular Brain Damage, Vascular Risk Factors, and Depression in Successful Cognitive Aging

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SUBCLINICAL VASCULAR BRAIN DAMAGE, VASCULAR RISK FACTORS,
AND DEPRESSION IN SUCCESSFUL COGNITIVE AGING

By

Jessica R. L. Warsch

A DISSERTATION

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of the University of Miami
in partial fulfillment of the requirements for
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SUBCLINICAL VASCULAR BRAIN DAMAGE, VASCULAR RISK FACTORS, AND DEPRESSION IN SUCCESSFUL COGNITIVE AGING

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Abstract of a dissertation at the University of Miami.

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Currently, about one in every eight Americans is age 65 or older; by the year 2050, it will be one in five people. Given this “graying” of the population, research into successful aging is of increasing relevance. The question of how to precisely define successful aging, however, has not been completely answered. Likewise, the role of vascular risk factors, subclinical vascular brain damage, and other biopsychosocial characteristics in normal cognitive aging are not well understood. This Dissertation focused on the identification of some of the physiological, behavioral, and social risk factors that distinguish people able to maintain extraordinary health at an advanced age.

Specifically, we aimed to create an ecologically valid definition of successful aging that incorporates both physical well-being and cognitive abilities, and to report the prevalence of successful cognitive aging in a population-based multi-ethnic cohort of older adults. We sought to describe how the prevalence varies by several sociodemographic and psychosocial determinants, and to investigate global vascular risk, depressive symptomatology, and MRI markers of subclinical vascular brain damage as correlates of successful cognitive aging.
We observed the prevalence of successful cognitive aging to be 37% in the study sample (N=1,162) of a diverse racial/ethnic population in Northern Manhattan (NYC, NY). The prevalence decreased with increasing age; we did not observe any differences by racial/ethnic group, but did note a lower prevalence with lower socioeconomic status. Several social resources and self-reported quality of life were related to successful cognitive aging, and appeared more important than demographic variables alone. We found that the likelihood of successful cognitive aging decreases with increasing global vascular risk score, more severe depressive symptomatology, and greater white matter damage.

The field of successful aging requires further study. Consideration of such biopsychosocial factors as socioeconomic status, social support, quality of life, and depressive symptoms alongside novel indicators of disease and disability including global vascular risk and white matter hyperintensity burden is essential. It may lead to a more robust definition of successful cognitive aging replete with opportunities to modify the aging process, as many of the factors investigated in this study are modifiable.
ACKNOWLEDGMENTS

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Jessica Warsch
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Chapter I. Introduction

1.1 Overview

Over 37 million Americans are age 65 or older, with that number projected to double by the year 2030 (He et al., 2005). An estimated 80% of this group has at least one chronic health condition, with 40% suffering from functional disabilities linked to coronary heart disease, stroke, hypertension, cancer, diabetes, arthritis, and cognitive impairment (CDC, 2008). Given the needs of our burgeoning elderly population, as well as the social and economic implications of an aging population, research into successful aging is of clinical, scientific, economic, and even political relevance.

As aging is not necessarily a deterministic, unidirectional process, but rather a much more complex phenomenon, the question of how to precisely conceptualize aging as successful, average, or disease-related has not been completely answered. Likewise, the role of vascular risk factors, subclinical vascular brain damage, and other biopsychosocial characteristics (e.g., comorbid conditions, depression, level of social support, and quality of life) in normal cognitive aging are not well understood. Based on the National Institute of Neurological Disorders and Stroke (NINDS) and National Institutes of Health (NIH) Staff Workshop which was convened toward developing a Blue Sky Vision for the Future of Neuroscience, NINDS staff have identified understanding the healthy nervous system as a key topic area, with an eye toward “understand[ing]
the natural aging process” and toward “determin[ing] the interactions between the healthy brain and body” (NINDS and NIH Staff Workshop, 2007).

By pinpointing those modifiable risk factors that influence the course of aging, particularly those that are common to cerebrovascular disease and cognitive impairment, we may both increase the number of years lived free of disability, as well as promote longevity in the aging population.

1.2 Specific Aims and Hypotheses

This study examined the determinants of successful cognitive aging in the Northern Manhattan Study (NOMAS). The study had four more specific aims:

Aim 1. Determine the prevalences of successful cognitive aging and cognitive decline (defined in 3.4.1 Chapter IV Methodology) in a community-based multi-ethnic cohort of stroke-free older adults.

Hypothesis 1. The prevalence of successful cognitive aging will be lower with advancing age and for blacks and Hispanics (compared to non-Hispanic whites), and greater for women (compared to men).

Aim 2. Examine the sociodemographic determinants (education and literacy, social support, and health insurance status) of successful cognitive aging and differences in quality of life measures in a community-based multi-ethnic cohort of stroke-free older adults.
Aim 3. Investigate the relationship between cerebrovascular risk factors, as measured by global vascular risk, and depressive symptomatology with successful cognitive aging.

Hypothesis 3a. Lower NOMAS global vascular risk score (GVRS) will be associated with successful cognitive aging.

Hypothesis 3b. Depressive symptoms will be inversely associated with successful cognitive aging, adjusting for sociodemographic and vascular risk factors.

Aim 4. Investigate brain morphology and subclinical vascular damage as correlates of successful cognitive aging.

Hypothesis 4. Subclinical markers of neurodegeneration and vascular disease, as measured by brain atrophy, ventricular enlargement, white matter hyperintensity volume and subclinical infarction, will be inversely associated with successful cognitive aging, after adjusting for sociodemographic factors and vascular risk.

1.3 Organizational Outline

Background on successful cognitive aging, and on vascular risk, subclinical vascular brain damage, and depression as they relate to aging, including a review of the literature and the significance of this study, is presented in Chapter II. Methodology and statistical analyses are described in Chapter III. Four chapters encompassing work we have performed to evaluate the
determinants of successful cognitive aging in the Northern Manhattan Study form the body of this dissertation. The first chapter is entitled, “The Prevalence of Successful Cognitive Aging in the Northern Manhattan Study Multi-ethnic Cohort”; the second chapter is entitled, “Sociodemographic Determinants of Successful Cognitive Aging and Differences in Quality of Life”; the third chapter is entitled, “Global Vascular Risk, Depressive Symptomatology, and Successful Cognitive Aging”; and the fourth chapter is entitled “Subclinical Vascular Brain Damage as a Correlate of Successful Cognitive Aging.” Key findings and conclusions, study limitations, and recommendations for future research are discussed in Chapter VIII.
Chapter II. Background

2.1 Successful Aging

Successful aging has been characterized as “the ability to maintain three key behaviors or characteristics: a low risk of disease and disease-related disability; high mental and physical function; and active engagement in life” (Rowe and Kahn, 1998). While common changes are experienced by everyone, no simple chronological timeline of aging exists. Life expectancy in the U.S. has increased from 47 years for Americans born in 1900, to 77 years for those born in 2001 (CDC, 2003). Unfortunately, living longer has not been synonymous with living well. The State of Aging and Health in America 2007 report identifies the prevention of cognitive decline as a key area in which the public health arena can help to make significant improvements in quality of life (CDC, 2007). In this study, we identified some of the physiological, behavioral, and social risk factors that distinguish people able to maintain extraordinary health at an advanced age from ones who experience physical and/or functional decline earlier in life.

2.2 The Aging Population

Older adults, age 65 and above, currently represent 12.4% of the U.S. population, or about one in every eight Americans – an increase of 10% since 1996, and of 200% since 1950 (AoA, 2008; US HR, 1988). Approximately 75 million Americans were born between 1946 and 1964, and these “baby boomers” represent over one-third of our population; by the year 2050, one in three
Americans will be over 55 years old, and one in five over 65 years old (Figure 2.1) (AoA, 2001). Those aged 85 years and older (the “oldest old”) constitute the fastest growing segment of the population, numbering 5.3 million in 2006, and projected to increase to 8.9 million by 2030 (AoA, 2008).

America’s older adult population is fast becoming more racially and ethnically diverse: the present population growth rate for whites is 6.5%, for blacks 12.7%, for Hispanics 29%, and for Asians 31.3% (AoA, 2003). At the same time, the burden of many chronic diseases and conditions is shared disproportionately by minority populations. According to the 2004 National Health Interview Survey (NHIS), 39% of non-Hispanic white adults aged 65 years or older report very good or excellent health, compared with just 24% of non-Hispanic blacks and 29% of Hispanics (CDC, 2009). Moreover, older adults may experience the deleterious effects of health disparities more dramatically than any other age group, as they are more likely to have a chronic illness and often require more frequent contact with the healthcare system; therefore, the care and management of those older adults who are members of an ethnic community is a pressing priority.

With the cost of providing healthcare for an older American three to five times greater than that for someone younger than age 65, these demographic shifts will contribute to a projected 25% increase in our nation’s healthcare spending by 2030 (CDC, 2007). Given this “graying” of the population, and the adjustments it demands from our healthcare delivery system, the importance of health promotion and prevention is clear. The first goal of Healthy People 2010,
in fact, is to "help individuals of all ages increase life expectancy and improve their quality of life" (USDHHS, 2000).

In spite of the breakneck speed at which progress has been made with respect to our understanding of the biological basis of this dynamic process, the keystones of aging and longevity have yet to be uncovered. By distinguishing successful agers from at-risk populations, identifying cognitive patterns characteristic of successful aging, and elucidating links to physical, social, and psychological factors, we may better understand – and be better equipped to respond to – the challenges of our aging nation. This study is aligned with the mission of The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health with respect to reducing the burden of neurological disease by aiming to contribute to the field a better understanding of the role of important risk factors such as vascular disease, depression, and cognitive reserve in successful cognitive aging using quantitative measures of cognitive performance and brain morphology (CDC and Alzheimer's Association, 2007).

2.3 Vascular Cognitive Impairment

Cognitive impairment is part of the clinical presentation of several syndromes associated with vascular brain disease. However, the precise frequency of cognitive impairment attributable to cerebrovascular disease is difficult to ascertain, largely because diagnostic criteria often underestimate its prevalence. Current definitions are inadequate for several reasons. First, vascular disease may affect cognition in ways that have been systematically
underestimated due to the historical evolution of diagnostic criteria for both Alzheimer disease (AD) and vascular dementia (VaD) (Bowler, Steenhuis & Hachinski, 1999). Thus, the phenotype is not well understood. Next, dementia implies a functional decrement of sufficient severity to interfere with activities of daily living; but, in order to develop effective primary prevention efforts, a less restrictive definition that would allow for the detection of disease prior to dementia is needed. Lastly, vascular and degenerative causes of dementia are often commingled because they are both prevalent in the elderly. Many individuals with AD, especially those over the age of 85, show vascular pathology to the extent that they would more accurately be characterized as having “mixed vascular-AD dementia,” but are difficult to classify without neuroimaging or pathological data (Langa, Foster & Larson, 2004).

The term “vascular cognitive disorder” was proposed as a way of defining cognitive disorders with a vascular contribution, and was intended to cover a spectrum of impairment from mild to dementia (Sachdev, 1999). To be able to identify cognitive deficits early enough to intervene, it was useful to term the mildest stage of vascular cognitive impairment as “vascular cognitive impairment no dementia” (vCIND) (Black, 2007). The prevalence of vCIND may be as much as three million in the United States – as high as that for vascular cognitive impairment with dementia – but the true public health impact remains unknown (Leblanc, et al., 2006). Vascular cognitive impairment is a critical premise as it avoids a priori assumptions about the phenotype that is created by vascular disease; such assumptions have driven the development of case definitions for
VaD that are currently in wide usage. This was a consequence of the fact that early definitions of VaD were modeled after AD, and disproportionately emphasized deficits in memory. Since the effect of vascular disease on cognition may not fit the pattern of damage to the hippocampus and related circuits seen in AD, such definitions confound attempts to define vascular phenotypes of cognitive impairment (Erkinjuntti et al., 1997; Looi & Sachdev, 1999). Methodological considerations are another reason why the specificity of the cognitive profile of vascular cognitive impairment has not been completely resolved – many of the studies with detailed neuropsychological testing have been limited by their modest sample size, and some cognitive domains, such as psychomotor speed and executive function, have not been explored in sufficient detail – underscoring the need for further research (Garrett et al., 2004; Laukka EJ et al., 2004; Tierney et al., 2001; Wright et al., 2008).

2.4 Cerebrovascular Risk Factors and Cognitive Aging

The NINDS Stroke Progress Review Group (SPRG) posed the questions, “What role do cardiovascular disease risk factors…play in cerebrovascular biology? How do these risk factors interact with each other and with the process of aging?” and Priority 3 of the NINDS SPRG specifies the goal of elucidating the “determinants of cerebral vascular aging” (SPRG, 2002). Indeed, vascular risk factors produce deleterious effects on brain function via overt strokes, but subclinical vascular brain lesions are now becoming recognized as highly prevalent in older populations and may have cognitive consequences that are not
fully appreciated (Knopman et al., 2001). Ultimately, as many cerebrovascular risk factors are preventable and treatable, a better understanding of the pathophysiology of vascular cognitive impairment may lead to identification of targets for reducing vascular cognitive impairment and encouraging successful aging.

A number of epidemiologic studies have demonstrated a strong association between elevations in middle-life blood pressure and subsequent cognitive impairment and dementia (Birns & Kalra, 2009). However, in older age, low blood pressure may be associated with an increased risk of dementia (Vergheese et al., 2003). Several population-based studies have shown associations between measures of diabetes mellitus and cognitive impairment, “dementia with stroke,” and AD, though few have specifically addressed the relationship between fasting glucose levels and measures of insulin resistance on patterns of cognitive dysfunction (Luchsinger et al., 2001). Hyperlipidemia, as well, has been shown to be related to cognitive decline and the risk of dementia (Hayden et al., 2006). In NOMAS, blood pressure and hypertensive medication use, fasting blood glucose and diabetes medication use, and lipid levels and cholesterol medication use have all been measured. Smoking habits and history of cardiac disease are also well documented. However, as these known modifiable cerebrovascular risk factors do not account completely for overall risk, the identification of novel exposures and markers of disease that may help to identify those people more prone to cognitive impairment is imperative (Braunwald, 1997; Haidari et al., 2001a, 2001b). Elevated homocysteine, insulin
resistance and the metabolic syndrome, alcohol consumption, and markers of inflammation have all been associated with poorer cognitive performance, and NOMAS participants have been characterized with respect to these measures (Elias et al., 1999; Lehmann, Gottfries & Regland, 1999; Luchsinger, 2008; McCaddon et al., 2001).

Recently, chronic kidney disease (CKD), too, has been proposed as an important independent risk factor for cerebrovascular disease, and studies have demonstrated a link between CKD and cognitive impairment. The prevalence of cognitive impairment and dementia in end-stage renal disease (ESRD) is more than twice that of the general population, and earlier stages of CKD as well have been associated with an increased risk for cognitive impairment (Fukunishi et al., 2002; Seliger et al., 2004). The Health, Aging, and Body Composition Study found that CKD is associated with an increased risk for cognitive impairment in the elderly that cannot be fully explained by other well-established risk factors (Kurella et al., 2005). Kidney disease may represent an additional mechanism leading to cognitive impairment, and could present a target for earlier intervention.

Consideration of constellations of vascular risk factors rather than individual factors, though, may be more relevant (Sacco, 2007). With cardiovascular diseases and stroke as the number one and three causes of death in the United States, much attention has been paid to the development of models to predict who may be at increased global vascular risk, which encompasses a variety of adverse vascular outcomes (Heron et al., 2009). The
use of such tools has been recommended to help identify individuals who could benefit from therapeutic interventions and who may not otherwise be treated on the basis of any one risk factor (Goldstein et al., 2006). Various models have been developed, with the Framingham-based being the most widely studied and utilized (D'Agostino et al., 1994; D'Agostino et al., 2008; Wilson et al., 1998). However, few are designed to estimate the global risk of myocardial infarction, stroke, or vascular death in multi-ethnic populations, and most do not include many behavioral variables or anthropometric indices (Assmann et al., 2002; D'Agostino et al., 1994; Ridker et al., 2007; Tanne et al., 1998). A global vascular risk score was recently developed using the NOMAS cohort that combines traditional, behavioral, and anthropometric risk factors, uses continuous variables for physiological parameters, and is applicable to non-white patient groups, presenting a more comprehensive approach to primary prevention (Sacco et al., 2009).

Few studies have examined the role of vascular risk factors in successful cognitive aging, and the well-characterized NOMAS sample has provided a unique opportunity to do so, with the current study having generated data suggestive of avenues for prevention and treatment of vascular cognitive impairment and which promote successful cognitive aging.

2.4 Subclinical Vascular Brain Damage and Cognitive Aging

The exact mechanisms through which the aforementioned cerebrovascular risk factors convey cognitive impairment are unknown, but
recent evidence suggests that risk factor-related structural brain changes are associated with cognitive changes (DeCarli, 2003). The introduction of more advanced brain imaging modalities has led to the definition of subclinical vascular brain damage, including white matter hyperintensities (WMH), which are areas of increased signal often found incidentally on Flair/T2-weighted MRI scans of the brains of clinically asymptomatic individuals, and subclinical infarcts, evidenced by radiologic or pathologic indicators of cerebral infarction in the absence of clinical symptoms (Bots et al., 1993). Growing evidence implicates WMH in cognitive functions, especially attention, psychomotor speed, and executive control, though the volume of injury sufficient to cause dysfunction is not known (de Groot et al., 2000; Wright et al., 2008). Likewise, subclinical thalamic infarcts have been found to cause memory dysfunction, and infarcts elsewhere have been associated with psychomotor slowing (Vermeer et al., 2003). There are limited data on the role of these subclinical findings in determining whether individuals remain cognitively normal as they age, especially in blacks and Hispanics.

That microvascular brain disease becomes increasingly common with advancing age has been demonstrated through neuroimaging (Ovbiagele & Saver, 2006). But, there is a need to examine patterns of cognitive function in relation to quantitative measures of WMH, subclinical infarction, and brain atrophy in order to capture the total burden of vascular brain disease. The recent NINDS CSN Harmonization Standards Report established guidelines for the MRI sequences to be acquired in research datasets and include measures of brain
atrophy, WMH, and subclinical infarction and hemorrhage (Hachinski et al., 2006). Each of the NINDS CSN recommended MR sequences was acquired in our NOMAS imaging protocol, providing an opportunity to characterize cerebrovascular brain damage associated with vascular cognitive impairment versus successful cognitive aging. In addition, measures of brain atrophy were used in combination with the other measures to help distinguish the role of degenerative processes from vascular ones.

2.5 The Vascular Depression Hypothesis

Depression is a major public health problem, and a leading predictor of functional disability and mortality. Affecting 3% to 5% of males and 8% to 10% of females in the United States, depression is associated with economic consequences of over 83 billion dollars annually (Coyne, Fechner-Bates & Schwenk, 1994; Kessler et al., 2005; Murphy et al., 2000). Depression likely represents a continuum of heterogeneous, yet phenotypically similar, biopsychosocial disorders, for which pathogenetic factors are vast and subject to individual variation. Psychosocial and genetic factors are thought to play a primary causal role in the occurrence of depression in early life; the origins of depression in older versus younger persons, however, may be less related to heritability (Ebmeier, Donaghey & Steele, 2006).

Because depressive symptoms are often comorbid with vascular disease and its risk factors, vascular depression has been proposed as a clinical subtype of major depression in later life (Alexopoulos et al., 1997). Support for this as a
specific diagnostic entity comes from findings that white matter hyperintensities occur in a subgroup of patients with geriatric depression, and reflect underlying cerebrovascular disease that predisposes them to depression by disrupting frontostriatal circuitry (Herrmann, Le Masurier & Ebmeier, 2008). On the other hand, WMH has been correlated in both depressed and non-depressed subjects with cerebrovascular risk factors, including hypertension, diabetes, history of myocardial infarction or coronary artery disease, and smoking (Kumar et al., 1997).

The vascular factors above have been implicated not only in depression, but also in another common geriatric syndrome, dementia. And, cognitive decrements in patients with late-life depression have been demonstrated across a variety of domains (including memory, attention, visuospatial ability, processing speed, and executive functioning), giving rise to the term pseudodementia (Wells, 1979). Whether impairments in these cognitive domains in depressed persons are mediated by vascular damage has not been fully elucidated. The association is further complicated by its bi-directionality: older adults with depression frequently report cognitive difficulties, and the prevalence of depression during dementia has been estimated to be as high as 86%, with depressive symptoms in some cases being the first indications of a dementing illness (Harwood et al., 2000; Kliegel & Zimprich, 2005; Jorm, 2000). While considerable observational evidence exists to support a correlation between vascular risk factors and risk of cognitive decline and depression, the true nature of this relationship has not yet been fully explained (Flicker, 2008).
2.6 Subclinical Cerebrovascular Disease, Vascular Risk Factors, Depression, and Cognitive Function in NOMAS

As part of a sub-study of NOMAS, 1,290 brain MRI scans were obtained to determine the prevalence of subclinical vascular brain damage in a clinically stroke-free population and to examine the cognitive correlates of this damage. A previous analysis was performed to determine the prevalence of subclinical vascular disease in the NOMAS cohort. Among 892 participants (mean age 71.3) who had undergone brain MRI scans at the time of this analysis, 158 (17.7%) had subclinical brain infarcts (13.5% had 1 lesion, 4.3% had >1 lesion). Prevalence of infarcts increased with age (<65 years: 9.7%; 65 to 75 years: 16.4%; >75 years: 26.1%), was increased among men (21.3% vs. 15.2% in women), and was increased among blacks (24.0% vs. 18.1% in whites and 15.8% in Hispanics) (Prabhakaran et al., 2008). The volume of white matter hyperintensities (WMHV) has also been determined to be similarly high in this group. The mean WMHV was 0.6 mL (SD 0.7, range 0.02-4.7 mL), and the prevalence of WMHV-large, defined as one standard deviation above the age-adjusted mean, was 17%, in line with the prevalence of subclinical brain infarction.

Equally important is the prevalence of vascular risk factors, as their relationship to subclinical vascular brain damage and impact on cognitive aging, described in detail in the above sections, is a critical component of this study. In the NOMAS MRI cohort, 94.5% of subjects have at least one vascular risk factor (hypertension, diabetes, cardiac disease, high cholesterol, or smoking).
Additionally, the prevalence of clinically significant depression, defined by a Center for Epidemiologic Studies Depression (CES-D) scale score above 15, in this group was 18.1%. This is important given that several of our brain MRI measurements have been associated with depression in independent studies, and because Aim 3 involved the association between successful cognitive aging and depressive symptomatology in older adults.

Also as part of the NOMAS MRI Study described above, a quantitative neuropsychological protocol was developed that meets the NINDS CSN Harmonization Standards for research into the effects of subclinical vascular disease on cognitive function published in 2006 (Hachinski et al., 2006). Preliminary data (N=478) on the association between WMHV and cognitive function were presented at the International Stroke Conference in 2006 (Wright et al., 2006a). Multivariate logistic regression was used to estimate the relationship between WMHV and cognitive function using tests of motor speed (grooved pegboard), attention (Color Trails 1), recognition memory (California Verbal Learning Test, CVLT), and delayed recall (CVLT), adjusted for sociodemographic variables and vascular risk factors. Older age, female gender, and Hispanics and blacks compared to whites had greater WMHV. Diastolic, but not systolic, blood pressure, as well as total homocysteine (tHcy), were positively associated with WMHV in a linear fashion. Worse performance on delayed recall of a 12-word list (Odds Ratio (OR)=1.3, 95% Confidence Interval (CI): 1.1-1.4) and performance on the grooved pegboard (OR=2.3, 95% CI: 1.0-5.4) were independently associated with WMHV. More recently, white matter hyperintensity
volume and subclinical infarction were examined in relation to performance on
tests of sequencing, cognitive flexibility, and sensorimotor ability in the NOMAS
cohort (Wright et al., 2008). Both subclinical infarcts and white matter
hyperintensity volume were associated with globally worse cognitive
performance; in particular, increasing WMHV was associated with reduced
cognitive flexibility and lower psychomotor speed.

In preliminary analyses, the NOMAS sample was restricted to those with
baseline Mini Mental State Exam (MMSE) scores above 26 in order to investigate
the characteristics of a subset of healthy cognitive agers. Of the 1,021 subjects
available for study, 663 (65%) had an MMSE score at or above 27; of those, 54%
were less than 65 years of age, 35% between the ages of 65 and 74, and 11%
75 or older; more than half (58%) had at least completed a high school
education. The sample was 53% Hispanic, with whites and blacks each
comprising 22%. Notably, 91% of whites and 75% of blacks met the MMSE
cutoff, compared to just 55% of Hispanics. This is an important finding, as
socioeconomic factors, particularly race/ethnicity and level of education, may
influence performance on the MMSE independent of other conditions; therefore,
the MMSE cutoff for this study was based on level of education (Tombaugh et al.,
1996).

A number of modifiable behavioral and cardiovascular risk factors have
been associated with maintenance of good health in older adults (Burke et al.,
2001). In the sample of individuals with normal baseline cognition from the
previously mentioned preliminary analysis, 66% of subjects had a history of
hypertension (systolic BP >140 mm Hg or diastolic BP >90), 13% had either a history of diabetes or a fasting blood sugar ≥126 mg/dL, 16% had a history of cardiac disease (angina, bypass surgery, angioplasty, atrial fibrillation, myocardial infarction, or valvular heart disease), and 8% had experienced a subclinical infarction per MRI analysis. Mean total cholesterol was 202.4 mg/dL, triglycerides 133.6, LDL 129.4, and HDL 46.8 (HDL2 = 14.3, HDL3 = 32.4). With respect to lifestyle factors, the group had an average body mass index of 27.8, 14% and 39% were current and former smokers, respectively, and over one-third (36%) were not physically active; 43% were moderate consumers of alcohol. Reported alcohol consumption, which had a J-shaped relationship with stroke risk in the NOMAS cohort, was also related to cognition; moderate alcohol consumption was inversely associated with having a low score on the MMSE (OR=0.78, p=0.02), controlling for age, education, whether or not persons had Medicaid, and other vascular risk factors, suggesting it may be protective (Wright et al., 2006b). A prospective study was carried out and found moderate alcohol intake to be protective against cognitive decline using the modified Telephone Interview for Cognitive Status (TICS-m), with no difference between carriers and non-carriers of the apolipoprotein E4 allele, arguing against an association with AD processes (Wright et al., 2006c).

Chronic kidney disease was found in NOMAS to be a significant risk factor for stroke and combined vascular events, especially in blacks (Nickolas et al., 2008). The presence of CKD, defined as a creatinine clearance (CCl) between 15 and 59 mL/min, was associated with a 43% increased stroke risk in the overall
cohort; blacks with a CCI between 15 and 59 mL/min had a significantly increased risk of both stroke and combined vascular outcomes (stroke, myocardial infarction, and vascular death). More recently, decreased kidney function was associated with cognitive decline even in those with mild CKD (Khatri et al., 2009). NOMAS participants with a CCI of <60 mL/min and those with a CCI between 60 and 90 mL/min performed significantly worse over time on the modified Telephone Interview for Cognitive Status than did those with a CCI >90 mL/min.

Because white matter hyperintensities appear to be more prevalent in depressed elderly persons, the association between WMHV and depressive symptoms was investigated in the NOMAS MRI cohort (Loring et al., 2009). The prevalence of clinically significant depression was 18% (N=1,075). Generalized linear models were fitted to examine log-transformed WMHV in relation to CES-D score. Greater WMHV was associated with more severe depressive symptomatology after adjustment for sociodemographic factors (p=0.0004); the findings remained after controlling for hypertension, history of coronary artery disease, diabetes, and smoking. As these results suggest that the relationship between WMHV and depression may not be mediated entirely by vascular risk factors, but perhaps by other mechanisms such as pro-inflammatory cytokines, more research is needed.
2.7 Unresolved Challenges

As life expectancy has increased, so, too, has the number of individuals living with chronic diseases. Many of these conditions, including heart disease, stroke, hypertension, diabetes, chronic kidney disease, and depression, among others, have been linked to cognitive impairment (Saczynski et al., 2008; Yaffe et al., 2004). A major component of successful aging is the avoidance of both physical disability and cognitive impairment, yet few studies have examined the mutual risk factors related to these two domains. Moreover, the basic pathophysiological mechanisms underlying various cerebrovascular diseases (e.g., inflammation, oxidative stress) may also be shared.

Although some studies have documented a relationship between these adverse outcomes and their shared risk factors, few population-based studies have included black and Hispanic individuals living in the same community, though the prevalence of depression, vascular risk factors, subclinical cerebrovascular disease, and risk of dementia and stroke may be higher in these groups than in whites (Brickman et al., 2008; Sacco et al., 2001b; Strine et al., 2008; Tang et al., 2001). Much of the research done on the effect of vascular risk factors on cognitive performance has been performed exclusively in white subjects, though Hispanics represent the most rapidly growing segment of the population (AoA, 2003). For instance, non-white populations have been underrepresented in studies such as Framingham and Rotterdam, and the Cardiovascular Health Study does not include Hispanics. Moreover, data on
vascular disease in Hispanics mostly reflects that of Mexican-Americans, and does not take into account the heterogeneity of the Hispanic population. This study benefited from the racial-ethnic mix of the NOMAS cohort, which is approximately 52% Caribbean Hispanic, 24% black, and 20% white.

The NINDS SPRG recommends “expanded use of…human studies to 1) define populations at high risk for vascular cognitive impairment progression, [and] 2) validate clinically meaningful radiographic endpoints…,” with an “overall goal…to lay the groundwork for…candidate prevention strategies” (SPRG, 2006). Evidence suggests that the promotion of a healthy lifestyle may mitigate chronic disease and changes in cognitive functioning. Therefore, identifying the underpinnings of combined cognitive and physical decline could present a prime opportunity for a multifaceted primary prevention paradigm, including risk factor modification or more aggressive treatment of comorbidities.
Figure 2.1. Percent of the population aged 60 and over, 65 and over, and 85 and over: 1900 to 2050

SOURCES

This chart was compiled by the U.S. Administration on Aging using the following Census data:


Projections for 2010 through 2050 are from: Table 12. Projections of the Population by Age and Sex for the United States: 2010 to 2050 (NP2008-T12), Population Division, U.S. Census Bureau; Release Date: August 14, 2008.
Chapter III. Methodology

3.1 Overview of Research Design and Methods

Chronic, comorbid, cognitive and physical impairments and their association with biopsychosocial factors are at the crux of this study; a model rooted in both empirical and theoretical evidence, it can be visualized in the conceptual framework (Figure 3.1) that follows at the end of this chapter (Engel, 1977). The present studies were completed using a secondary analysis of data collected for the ongoing Northern Manhattan Study (NOMAS). NOMAS is the first of its kind to investigate the determinants of vascular disease and stroke in Hispanic, black, and white subjects from the same community. It is an ideal sample to study normal cognitive aging for several reasons. First, the NOMAS prospective cohort is clinically stroke-free, and includes younger individuals likely to be either free from, or in the earliest stages of, vascular cognitive impairment. Second, conventional anthropomorphic and blood markers of vascular risk have been measured in detail, as have novel risk factors such as total homocysteine, insulin resistance and the metabolic syndrome; additionally, traditional and novel risk factors have been combined into a measure of global vascular risk. And, as research in NOMAS has shown that black and Hispanic subjects have a higher prevalence of vascular risk factors and subclinical vascular brain damage (Howard et al., 1998; Sacco et al., 1997; Sacco et al., 2001; Wright et al., 2005), and are at elevated risk of stroke compared to white subjects, we were able to examine the determinants of cognitive aging in these understudied populations.
who may be at greater risk. A description of the Northern Manhattan Study is below, followed by the individual methods used for each chapter in this work.

3.2 The Northern Manhattan Study

NOMAS is a population-based cohort study that includes 3,298 stroke-free participants identified from random digit dialing using dual-frame sampling to identify published and non-published telephone numbers. People were eligible if they had never been diagnosed with a stroke, were 40 years of age or older, and had been residents of Northern Manhattan for at least 3 months in a household with a telephone. Subjects from the telephone sample were recruited for in-person assessment and the overall response rate was 68%. The NOMAS study timeline is presented in Figure 3.2.

3.3 Measures/Assessments

3.3.1 Baseline Assessment, Sociodemographic Variables, and Risk Factors

Baseline data were collected between 1993 and 2001. All participants underwent a thorough baseline examination including a comprehensive medical history, physical and neurological examination by study physicians, review of medical records, and fasting blood samples for glucose and lipid measurements. Supplemental information was obtained through interviews by trained bilingual research assistants using validated data collection instruments.
Race and ethnicity were based on self-identification modeled after the United States Census categories: white, black or African-American, American Indian, Eskimo or Aleutian (Alaskan Native), Asian or Pacific Islander, or other; and Hispanic/Spanish origin (Sacco et al., 2001). The distribution at enrollment was approximately 63% Hispanic, 21% black, 15% white, and 2% other groups (Sacco et al., 1997). Whether or not a person had Medicaid was self-reported, and served as a proxy for socioeconomic status, as Medicaid eligibility criteria are related to family income and poverty levels established by the federal government. Education was defined by self-report of years of formal schooling.

Standardized questions about vascular risk factors were adapted from the Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS) as defined previously (Gentry et al., 1985; Sacco et al., 2001). Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg based on the mean of 2 blood pressure measurements, self-report of a diagnosis of hypertension, or reported medical treatment of this condition. Cardiovascular conditions recorded included myocardial infarction, coronary artery disease, atrial fibrillation, valvular heart disease, and peripheral vascular disease.

Diabetes was defined as a fasting blood glucose of 127 mg/dL, self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Fasting high density lipoprotein (HDL) and total cholesterol were obtained using a Hitachi 705 automated spectrometer, and low density lipoprotein (LDL) levels were derived from the Friedewald equation.
Smoking was defined as never-smoker, current (within the last year) smoker, or former smoker; amounts were collected as packs per day and number of years smoked. Using structured interviews adapted from food frequency questionnaires, data on alcohol use was obtained as usual number of drinks per day, week, or month, and drinking was defined as moderate if the subject reported drinking at least one drink per month, but no more than two drinks per day (Wright et al., 2006c). Leisure-time physical activity was recorded using a simple questionnaire adapted from the National Health Interview Survey (NHIS), and was operationalized as moderate to heavy versus mild or none based on the type and frequency of activities performed (Moss and Parsons, 1985).

3.3.2 Prospective Follow-Up

Subjects were followed annually by telephone. Changes in health or vital status, neurological or cardiac symptoms and events, and hospitalizations were assessed in the telephone interview. A positive screen for any potential cardiac or neurological event was followed by an in-person assessment to determine whether a vascular outcome had occurred.

3.3.3 MRI Examination

Subjects were enrolled into the MRI sub-study using the following criteria: (1) age older than 50 years; (2) no contraindications to MRI; and (3) willing to sign informed consent. The study was approved by the Columbia University Institutional Review Board. The Imaging was performed on a 1.5T MRI system.
(Philips Medical Systems) at the Columbia University Hatch Research Center. Analysis of WMHV was based on a Fluid Attenuated Inversion Recovery (FLAIR) image acquired in the Multi-Slice Turbo Spin Echo (MS-TSE) mode with a field of view of 250 mm, rectangular field of view of 80%, and an acquisition matrix of 192x133 scaled to 256x256 in reconstruction. The FLAIR image has a slice thickness of 3 mm with no gap, an echo time of 144 ms, a repetition time of 5500 ms, an inversion recovery delay of 1900 ms, and a flip angle of 90 degrees. Images were oriented parallel to a hypothetical line connecting the anterior and posterior commissures. For quantitative analysis of WMHV, MRI data were transferred to the University of California at Davis. Analyses were performed using the Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation. All analyses were performed blind to subject personal identifying information. White matter hyperintensity segmentation from surrounding tissue was performed in 2 steps according to previously reported methods (DeCarli et al., 1992, 1995, 1996). White matter hyperintensity volume was expressed as the proportion of total cranial volume to correct for head size and log-transformed to create a normal distribution (log-WMHV) for analysis as a continuous measure. The presence or absence of brain infarcts on MRI was determined according to a protocol using the size, location, and imaging characteristics of a lesion (DeCarli et al., 1999).

Complete MRI data were available for 1,290 individuals, 61% male, 15% white, 18% black, and 67% Hispanic, with a mean age of 70.6 ± 9.0 years. Just over 40% had less than eight years of education, and 47% had Medicaid.
3.3.4 Cognitive Assessment

Baseline cognitive function in NOMAS was assessed with the brief thirty-item Mini-Mental State Examination (MMSE) and was assessed again at the time of MRI (Folstein et al., 1975). The MMSE was administered in either English or Spanish by trained bilingual research assistants, depending on the language spoken by the subject at home. The MMSE assesses orientation, registration and recall of information, attention and calculation, and language; it has limited capacity to test frontal/executive and visuospatial functions (Woodford and George, 2007). Originally developed as a screening test to distinguish “organic” from “non-organic” cognitive disorders, the MMSE has more recently become a common instrument for screening for and monitoring the progression of cognitive impairment, though it is not diagnostic of dementia (Santacruz and Swagerty, 2001). While it has both a ceiling and a floor effect, the MMSE generally correlates well with other cognitive screening test scores and with a number of neuropsychological tests (Tombaugh, 1992).

3.3.5 Global Vascular Risk Score

While numerous tools have been developed for the purpose of estimating risk of coronary heart disease alone or stroke alone, risk prediction models for combined vascular outcomes (stroke, MI, vascular death) may be more useful (D’Agostino et al., 2008). A global vascular risk score (GVRS) was developed in NOMAS for assessing global vascular risk in its urban, multi-ethnic population
that incorporates traditional, behavioral, and anthropometric risk factors, utilizing continuous variables (Sacco et al., 2009). As the NOMAS score is derived from a multi-ethnic cohort, it may have improved applicability to non-white individuals compared to those tools derived from white or single gender populations.

A survival model was constructed to predict combined cardiovascular outcomes, which included stroke (ischemic or intracerebral hemorrhage), myocardial infarction (MI), and vascular death. Cox proportional hazard models were built by first including all of the traditional risk factors from the Framingham-based models (D’Agostino et al., 1994; D’Agostino et al., 2008; Wilson et al., 1998). Although certain variables were less predictive in the NOMAS cohort, they were retained since the goal was to build a predictor model adding to the traditional Framingham variables. Some traditional variables were used in a different functional form: diabetes was replaced by the continuous measure fasting blood sugar, and dichotomous smoking status was trichotomized as never, past, and current smoking. Basic sociodemographic variables (age, gender, and race-ethnicity) were retained, and other vascular risk factors that could be ascertained through history or blood tests were selectively added. Variables that were assessed included sibling history of stroke or MI, waist circumference, body mass index, waist-to-hip ratio, alcohol consumption, physical activity, peripheral vascular disease, atrial fibrillation, valvular heart disease, total homocysteine level, white blood cell count, and creatinine level. Risk factor variables that contributed significantly to model fit using the likelihood ratio criterion were kept. All two-way interaction terms, including by age, gender
and race-ethnicity, were examined, and the terms contributing significantly to the fit by the likelihood ratio criterion were included in the final model.

The GVRS was computed as shown in Table 3.1 according to the final model. In the NOMAS cohort, GVRS (calculated at baseline) ranged from 4.4 to 11.6 (mean 8.6 ± 1.0 standard deviation). Ten-year event-free probabilities were 0.95 for the first quartile of GVRS, 0.89 for the second quartile, 0.79 for the third quartile, and 0.56 for the fourth quartile (Sacco et al., 2009). The second to fourth quartiles had significantly different survival curves from the first quartile by logrank tests (p< 0.0001). A GVRS of 9.0 implied a 10-year probability of experiencing a vascular event of 0.20, a GVRS of 8.2 implied a 10-year probability of 0.10, and a GVRS of 6.6 implied a 10-year probability of 0.02. Thirty-five percent of our population had a GVRS of at least 9.0.

3.3.6 Depressive Symptomatology

Depressive symptoms were captured at baseline using the Hamilton Depression Rating Scale (HDRS) and at the time of MRI with the Centers for Epidemiological Studies Depression Scale (CES-D).

The HDRS, an interviewer-rated symptom inventory used in research to determine depression severity and response, was utilized to derive a measure of duration of depression (e.g., depressed at baseline as well as at time of MRI). Questions cover symptoms observed in depression such as low mood, insomnia, agitation, and anxiety, with each having between 3-5 possible responses increasing in severity; a cut-off point of 10 has been suggested for the
identification of depression (Hamilton, 1960 and 1967). Data were collected on antidepressant use as well, and were taken into account as a covariate.

The CES-D is one of the most widely used tools for the measurement of depressive symptomatology in the general population. It includes twenty items selected from previously validated, more comprehensive, depression inventories, that together comprise six scales reflecting the following major dimensions of depression identified from the clinical literature: 1) depressed mood, 2) feelings of guilt and worthlessness, 3) feelings of helplessness and hopelessness, 4) psychomotor retardation, 5) loss of appetite, and 6) sleep disturbances (Radloff, 1977). Response categories are designed to capture the frequency of depressive symptoms experienced within the past week, and are scored on a 4-point scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time). The total score is calculated from summing the scores from all items, and ranges from 0 to 60 points, with higher scores indicating more depressive symptoms.

3.4 Methods of Individual Chapters

The NOMAS database contained all of the necessary elements for this study. The analyses presented here were restricted to the aforementioned 1,290 participants in the NOMAS MRI sub-study. As a general consideration, SAS statistical software (version 9.2, SAS Institute, Cary, NC) was used for data management and all analyses and statistical tests. Significance was assessed according to a pre-set two-sided alpha level of 0.05 for all statistical tests.
The statistical power to accomplish some of our aims depended on unknown factors, given that this was the first study to combine this constellation of correlates of cognitive aging. However, we had the benefit of a substantial sample size, continuous risk factor and depression measurements, and quantitative structural imaging data to maximize our ability to correctly detect significant effects. Based on an estimated 30% prevalence of successful cognitive aging, our available sample of 1,290 subjects gave us 80% power to detect odds ratios of at least 1.4-1.5 for vascular risk, depressive symptoms, and subclinical vascular brain disease.

3.4.1 Chapter IV Methodology

Guided by Rowe and Kahn’s conceptualization of successful aging, as well as more recent attempts to examine the phenomenon in other large cohort studies (i.e., Depp & Jeste, 2006; Newman et al., 2003) we classified subjects based on disease, disability, and cognitive function. As about 75% of successful aging studies do not include a measure of “active engagement” as defined by Rowe and Kahn, we omitted this dimension so that we could investigate its association with successful aging in order to see whether its inclusion as a criterion for successful aging might be warranted (Depp & Jeste, 2006). More specifically, successful aging was defined as:
1) no history of cancer, chronic obstructive pulmonary disease, or cardiac disease (myocardial infarction, coronary artery disease, congestive heart failure, atrial fibrillation, or valvular heart disease);
2) a creatinine clearance rate of ≥45 milliliters per minute;
3) a global score of ≥95 on the Barthel Activities of Daily Living scale; and
4) an MMSE score of >17 for those with 8 years or less of education or >23 for at least 9 years of education.

Creatinine clearance rate was derived from the Cockcroft-Gault formula (Cockcroft and Gault, 1976):

\[
CCL = \frac{(140 - \text{age})}{(\text{serum creatinine in mg/dL})} \times \left(\frac{\text{weight in kg}}{72}\right) \\
\times (0.85 \text{ for women})
\]

Results from several large cohorts show that morbidity and mortality begin to rise at a GFR of 45 mL/min/1.73m² – the risks of death, cardiovascular events, and hospitalization rise sharply below this level, as do the odds of incident cognitive impairment (Etgen et al., 2009; Go et al., 2004; O’Hare et al., 2006). In light of such evidence, we chose this level as the cut-point instead of the traditional 60 mL/min/1.73m² criterion for CKD. It has been suggested that the National Kidney Foundation staging system for chronic kidney disease be amended since persons with stage 3 CKD (GFR 30-59 mL/min/1.73m²) comprise a
heterogeneous group with respect to their risk for each outcome (K/DOQI, 2002). In particular, stage 3 may be more informative if subdivided into early and late components, 3a (GFR 45-59 mL/min) and 3b (GFR 30-44 mL/min), in order to more precisely define the point at which mortality becomes the main concern (Abutaleb, 2007).

As the NOMAS MRI cohort included only stroke-free individuals, no history of stroke was an implicit criterion. Those with a history of seizures, convulsions, or epilepsy, or head trauma with loss of consciousness or memory, were excluded from analyses.

*Cognitive decline* was defined as a 3-point or greater decrease in MMSE score at follow-up, such that those initially defined as *successful agers* based on the criteria above and who did not meet this cut-off for cognitive decline were referred to as *successful cognitive agers* (Das et al., 1998; Kujawinski et al., 1993; Nguyen et al., 2003; Yaffe et al., 1999). Unadjusted differences in the prevalence of successful cognitive aging by decade of age, gender, and race/ethnicity (white, black, and Hispanic), were assessed by cross-tabulating the data and performing the chi-square ($\chi^2$) test; the difference in the mean age of the group that experienced successful cognitive aging and the group that did not was assessed with Student's $t$ test.
3.4.2 Chapter V Methodology

Chapter V addresses the role of the sociodemographic characteristics of education and literacy, social support, and health insurance status, as well as quality of life, in successful cognitive aging. Education was defined by self-report of years of formal schooling. Literacy was assessed with the reading subtest of the Wide Range Achievement Test – Third Edition (WRAT-3) for English speakers (Wilkinson, 1993). The WRAT-3 reading test, comprised of 55 words, is useful in the assessment of literacy levels among multi-ethnic populations, and has been validated for use in older adults (Ashendorf et al., 2009; Cosentino et al., 2007). This was particularly relevant to the current study because literacy level, as determined by WRAT-3 Reading performance, may be a better predictor of memory decline than years of education (Manly et al., 2003). Spanish speakers were administered the Word Accentuation Test (WAT), which consists of 30 infrequent Spanish words written without an accentuation mark (Del Ser et al., 1997). The WAT was designed to be equivalent to English language measures of reading recognition, and, similar to the WRAT-3, has been correlated with cognitive performance (Manly et al., 2004). For both tests, participants were instructed to read the words aloud to the examiner, and the total number pronounced correctly was used as the measure of literacy. Health insurance status was attained by self-report of having Medicaid, Medicare, and/or private insurance. Social support and quality of life were measured with selected questions from the NOMAS Social Resources and Functional Assessment Forms, respectively. Social support measures included in this study were marital
status, number of times spent talking on the telephone, number of friends, number of visits with friends/family, seeing friends/family as often as one would like, having someone to trust and confide in, feeling lonely, and having someone to help if one were sick or disabled. Five quality of life domains were assessed: activity, daily living, health, support, and outlook. The total quality of life score was computed by summing the scores from each of the five domains. Differences in the prevalence of successful cognitive aging were analyzed with the \( \chi^2 \) test for categorical variables (health insurance status, social support measures, and quality of life domains), and by Student’s t test for continuous variables (education, level of literacy, and total quality of life score).

In order to investigate the influence of multiple sociodemographic factors on successful cognitive aging simultaneously, a multivariate logistic regression model was built containing those variables that were statistically significant (\( p \leq 0.20 \)) in univariate analyses in this and the previous chapter as predictors of the dichotomous outcome variable successful cognitive aging (yes/no).

3.4.3 Chapter VI Methodology

This chapter explores the relationship between cerebrovascular risk factors, depressive symptomatology, and successful cognitive aging.

Logistic regression was employed to examine GVRS (calculated at the time of MRI) as a predictor of the dichotomous outcome variable successful cognitive aging (yes/no). Section 3.3.5 describes the GVRS in detail. Generalized linear models (PROC GENMOD, logit link function) were used for the regression,
adjusting for duration of follow-up time (time between baseline assessment and MRI), with other covariates being those that were statistically significant (p≤0.20) in univariate analyses and which were not already included as a component of the GVRS.

The CES-D form provided the ability to examine depression as a continuous variable, an ordinal variable (quintiles of depressive symptoms), and a dichotomous variable (the recognized cutoff for clinically significant depression is CES-D ≥16) (Radloff, 1977). Logistic regression was employed to examine CES-D score as a predictor of the dichotomous outcome variable successful cognitive aging (yes/no). Additionally, HDRS total score, and a dichotomous composite measure created from CES-D and HDRS cut-off criteria (not depressed at baseline nor at MRI; depressed at baseline but not at MRI, depressed at MRI but not at baseline; depressed at baseline and MRI), were both tested in logistic regression analyses as predictors of successful cognitive aging to look at the effect of duration of depression. Generalized linear models (PROC GENMOD, logit link function) were used for the regression models. GVRS was included to account for vascular risk, with other covariates being those that were statistically significant (p≤0.20) in univariate analyses and which were not already included as a component of the GVRS. Antidepressant use (yes/no) and duration of follow-up time were taken into account in all models.
3.4.4 Chapter VII Methodology

Brain morphology and subclinical vascular damage were examined as correlates of successful cognitive aging in Chapter VII. Subclinical markers of neurodegeneration and vascular disease used were white matter hyperintensity volume, subclinical infarction, brain atrophy, and ventricular enlargement. As previously mentioned, WMHV was examined as a continuous measure (log-transformed to normalize the distribution), while subclinical infarction was considered as present or absent. Brain atrophy and ventricular enlargement (log-transformed) were examined as continuous variables. Logistic regression was employed to examine each of the four subclinical markers as a predictor of the dichotomous outcome variable successful cognitive aging (yes/no). Generalized linear models (PROC GENMOD, logit link function) were used for the regression analyses. GVRS was included to account for vascular risk, with other covariates being those that were statistically significant (p≤0.20) in univariate analyses and which were not already included as a component of the GVRS. Duration of follow-up time was taken into account in all models.

3.5 Privacy and Data Confidentiality

As per NOMAS protocol, each subject was assigned a unique identifier number at the time of enrollment and the code as well as all subject charts are kept at Columbia University, New York, NY. The key to the identified code is kept in a password-protected file at Columbia University as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized
access. Subjects were not identified by name, social security number, address, telephone number, or any other direct personal identifier in the data provided to the University of Miami. The personal identifying codes reside at Columbia University and are not accessible to the research personnel at the University of Miami. The research for this dissertation involved the study of existing data, and all data obtained were used for analysis purposes only (University of Miami Institutional Review Board #20070212). These data were maintained in the locked office of the investigator located in the Clinical Research Building, 13th floor, 1120 NW 14th Street, Miami, Florida.
Figure 3.1. Conceptual Framework
Figure 3.2. NOMAS Data Collection Timeline
Table 3.1. NOMAS Global Vascular Risk Model

<table>
<thead>
<tr>
<th>New Risk Factor Variables</th>
</tr>
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<tbody>
<tr>
<td>Waist (inches)</td>
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<tr>
<td>Moderate alcohol consumption</td>
</tr>
<tr>
<td>Moderate-to-heavy physical activity</td>
</tr>
<tr>
<td>Moderate-to-heavy physical activity * male gender</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>Sociodemographic Variables</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Black race</td>
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<tr>
<td>Hispanic ethnicity</td>
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<tr>
<td>Male gender</td>
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<tr>
<td>Traditional Risk Factor Variables</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Diastolic blood pressure * anti-hypertensive medication</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dL)</td>
</tr>
<tr>
<td>Former smoking</td>
</tr>
<tr>
<td>Current smoking</td>
</tr>
<tr>
<td>Total cholesterol:HDL (mg/dL)</td>
</tr>
</tbody>
</table>

**NOMAS GLOBAL VASCULAR RISK SCORE =**

\[
\text{Age} \times 0.08338 + \text{Male Gender} \times 0.37949 + \text{African American} \times 0.02770 + \text{Hispanic Ethnicity} \times -0.22214 + \text{Waist (inches)} \times 0.02156 + \text{Moderate alcohol consumption} \times -0.18039 + \text{Former smoking} \times 0.16383 + \text{Current smoking} \times 0.69142 + \text{Moderate-to-heavy physical activity} \times -0.16333 + \text{Moderate-to-heavy physical activity * male gender} \times -1.01324 + \text{Systolic blood pressure (mm Hg)} \times 0.00158 + \text{Diastolic blood pressure (mm Hg)} \times 0.01195 + \text{Diastolic blood pressure * anti-hypertensive medication} \times 0.00247 + \text{Peripheral vascular disease} \times 0.26737 + \text{Fasting blood sugar} \times 0.00432 + \text{Total Cholesterol:HDL (mg/dL)} \times 0.05678
\]
4.1 Overview

The percentage of the United States population aged 65 years and older will soon become greater than it has been at any other point in recent history, reaching 20% by 2050, a five-fold increase from the start of the twentieth century (He et al., 2005). It has also been suggested that if the rate of increase in life expectancy in developed countries over the past two centuries continues through the twenty-first century, most babies born since 2000 will celebrate their 100th birthdays (Christensen et al., 2009). As a result, the focus on extending life has shifted from late to improving quality of life.

Rowe and Kahn distinguished between “normal agers,” who experience a constellation of changes that convey a higher risk of disease or dysfunction, and “successful agers,” who are able to avoid disease and disability and maintain a higher level of physical and cognitive functioning (Rowe and Kahn, 1998). It is becoming increasingly important to determine the factors that promote optimal cognitive function in older age. Many older persons complain about their cognitive functioning, and cognitive impairment is associated with increased risk for progression to dementia, and contributes to decreased quality of life, increased neuropsychiatric symptoms, increased disability, and greater health care costs (Albert et al., 2002; Lyketsos et al., 2002; Peterson, 2004; Ponds and Jolles, 1996). While many researchers have documented that advancing age is
associated with diminishing cognitive function, the majority of previous studies of successful aging have not considered cognitive performance; the few that have incorporated measures of cognition into their models did not identify those biopsychosocial factors which predict successful cognitive aging (Depp and Jeste, 2006; Habib et al., 2007).

The key objectives of this study were to (1) propose a framework for successful aging that incorporates both physical well-being and cognitive abilities, to (2) estimate the overall prevalence of successful cognitive aging in a large cohort of multi-ethnic older adults, and to (3) measure the extent to which the prevalence varies by age, gender, and race/ethnicity.

4.2 Results

4.2.1 Sample Characteristics

Of the 1,290 individuals in the NOMAS MRI sub-study cohort, 1,162 (90%) had complete data necessary to determine successful cognitive aging status. Demographic characteristics of the sample are displayed in Table 4.2.1, and did not differ significantly from the overall MRI sub-study cohort. The average age of participants was 70.3 ± 8.9 years, with 50.9% between ages 70 and 96. Females comprised 61.2% of the sample. White and black adults represented 13.5% and 16.3%, respectively, while 69.9% of individuals were Hispanic. The mean difference in time between the baseline MMSE and follow-up MMSE was 6.1 ± 3.5 years.
4.2.2 Prevalence of Successful Cognitive Aging

The prevalence of successful cognitive aging among the 1,162 persons with complete data in the NOMAS MRI cohort was 37%. The proportion of older adults meeting the disease and disability criteria was 49%, and 87% met the cognitive criteria (Table 4.2.2). Of those who did not meet criteria for successful cognitive aging, the percentage with events in each domain were as follows (with lack of success in multiple areas possible): cancer, 7%; chronic obstructive pulmonary disease, 9%; cardiac disease, 17%; CCI <45 mL/min, 18%; Barthel ADL score <95, 6%; baseline MMSE <17 for ≤8 years of education or <23 for ≥9 years of education, 4%; ≥3-point decline on MMSE at follow-up, 11%.

4.2.3 Prevalence of Successful Cognitive Aging by Demographic Criteria

The prevalence of successful cognitive aging varied across demographic subgroups (Table 4.2.3). Participants who were successful, were, on average almost one year younger than those who were not (69.8 versus 70.7 years). The prevalence of successful cognitive aging differed significantly among age groups (p<0.0001). Excluding those aged less than 60 years, the prevalence of successful cognitive aging declined with age: 44% of those aged 60-69 years, 40% of those aged 70-79 years, and 28% of those aged 80 years or older were classified as successful cognitive agers. Individuals 50-59 years of age comprised less than 10% of the sample, and a smaller percentage was successfully cognitively aging as compared to all age brackets but the oldest.
Given the small proportion of subjects in the 50-59 year old group, we re-categorized subjects into groups of less than 64 years, 65-74 years, 75-84 years, and 85 or more years of age. Individuals in the youngest age group now comprised 28.2% of the sample, and those in the oldest just 6.5%, but a smaller percentage was still successfully cognitively aging as compared to all age brackets but the oldest.

Women were significantly less likely than men to be categorized as successful cognitive agers (34% versus 43%; p<0.001). Among women as compared to men, a greater proportion was in the youngest (11.3% vs. 7.3%; p=0.03) as well as oldest age groups (20.3% vs. 13.8%; p=0.005). We therefore examined the prevalence of successful cognitive aging by gender, stratified by age group (Table 4.2.4). We did not find any significant differences in the prevalence of successful cognitive aging by gender within any of the age groups.

There were no significant differences in the prevalence of successful cognitive aging by race/ethnicity. In our sample, race/ethnic groups differed significantly by age (p<0.0001): Hispanics tended to be younger (55% were aged 69 or lower), and blacks and whites older (just 35% and 31% were aged 69 or lower, respectively). We therefore examined the prevalence of successful cognitive aging by race/ethnicity, stratified by age group (Table 4.2.4). Again, we did not find any significant differences in the prevalence of successful cognitive aging.
4.3 Discussion

Successful cognitive aging is a multidimensional construct for which there is no currently accepted standardized definition. For this study, we created a definition of successful aging that incorporates both physical well-being and cognitive abilities. We reported the overall prevalence of successful cognitive aging in a large cohort of multi-ethnic older adults, and described the extent to which the prevalence varies by age, gender, and race/ethnicity.

We defined criteria for successful cognitive aging based on an often-used outline of reaching old age without suffering form a serious chronic illness, while having maintained high levels of physical and cognitive functioning (Reed et al., 1998; Seeman et al., 1994). We considered only those diseases that are major causes of mortality among older adults – cancer, chronic lung disease, heart disease, and stroke. Additionally, we refined our definition as compared to those used in previous studies by including chronic kidney disease as a novel component. The prevalence of CKD has increased over the past decade to 13% in the U.S., and it is associated with cognitive impairment, dementia, disability, and death (Coresh et al., 2007).

We assessed baseline cognitive status and cognitive decline with the Mini-Mental State Examination, which is used widely in epidemiological field studies (Folstein et al., 1975). Lower cut-offs to indicate impairment have been recommended for the elderly, as MMSE scores generally decline with advancing age (Folstein et al., 1985; MacKenzie et al., 1996). And, scores on the MMSE
have repeatedly been shown to be related to level of education in both clinical and community samples and among minority as well as non-minority groups (Fillenbaum et al., 1990; Murden, 1991). To avoid misclassification of older adults with low education, we developed cognitive criteria for successful cognitive aging as a MMSE score of >17 for those with 8 years or less of education and >23 for those with at least 9 years of education.

The results of this study indicate that just less than 40% of NOMAS MRI sub-study participants experienced successful cognitive aging. This estimate is lower than the 50% observed in a similar study of successful cognitive aging from the Cardiovascular Health Study (CHS) Research Group (Newman et al., 2003). The discrepancy is likely accounted for by variation in measurement of the components of successful cognitive aging. We expanded upon the definition used in the CHS by adding chronic kidney disease, and used education-adjusted cut-offs for cognitive impairment. Another reason for the lower prevalence in our study could be a difference in sample racial/ethnic composition; however, as race/ethnicity was not significantly associated with successful cognitive aging, the heterogeneity of our sample compared to that of the CHS is unlikely to be the key factor. Despite variability among definitions, our findings add to the growing body of literature that suggests that the vast majority of older adults are not successfully aging (Depp and Jeste, 2006).

Not surprisingly, the prevalence of successful aging decreased with increasing age as we hypothesized, starting at age 60, with the sharpest decline in the oldest old aged 80 and above. We found that a smaller proportion of those
individuals in the youngest age group (50 to 59 years), as compared to all groups but the oldest, were less likely to be classified as successful cognitive agers. Post-hoc analyses showed that a significantly lower percentage of participants aged 50 to 59 years met the disease and disability criteria as compared to those aged 60 and above (27% versus 51%; p<0.0001), but a greater percentage met the cognitive criteria (96% versus 86%; p=0.004). With less than 10% of our sample younger than 60 years, however, we re-categorized subjects into groups of less than 64 years, 65-74 years, 75-84 years, and 85 or more years of age. Individuals in the youngest age group now comprised 28.2% of the sample, and those in the oldest just 6.5%, but a smaller percentage was still successfully cognitively aging as compared to all age brackets but the oldest.

We found that, similar to our overall sample, the successful cognitive aging group includes a greater percentage of women than men (55% vs. 45%). Given that age is one of the strongest predictors of successful cognitive aging, and that because survivorship is greater among women they comprise a higher percentage of the oldest age categories, such a result would be expected and has been reported on previously (He et al., 2005; Newman et al., 2003). Indeed, in our sample, a greater proportion of women as compared to men were aged 80 or older (11.3% vs. 7.3%), or 59 or younger (20.3% vs. 13.8%). Given that we did not find any significant differences in the prevalence of successful cognitive aging by gender when stratifying by age group, it is less likely that age explains our findings with respect to gender. Interestingly, our between-gender comparison showed that women were significantly less likely than men to be
categorized as successful cognitive agers. Women typically report more chronic conditions and functional impairments than men, and experience more disability, and may thereby be aging less successfully (Newman and Brach, 2001).

We did not observe any differences in the prevalence of successful cognitive aging by racial or ethnic groups. This may be explained by the fact that the confounding of race and socioeconomic status is a common problem in health disparities research (LaVeist, 2005). Other studies have shown that social resources, and more specifically, socioeconomic status, may be responsible for racial-ethnic differences in mortality and successful aging (Boden-Albala et al., 2005; Hayward et al., 2000). Social resources and socioeconomic status appear to be more important for successful cognitive aging than race or ethnicity in this sample, and are discussed in the next chapter.

4.4 Limitations

The use of a community-based multi-ethnic sample gave us the ability to study a representative range of physical and cognitive health components and sociodemographic characteristics of older adults, though there are several limitations to our study that are worth noting. The NOMAS MRI sample suffers from a healthy volunteer survivor bias, as the sub-study participants are somewhat healthier than the overall prospective cohort. Also, the manner in which successful cognitive aging is defined and measured undoubtedly impacts prevalence estimates and observed associations. For example, a more strict definition inclusive of a greater number of chronic health conditions would have
resulted in a lower prevalence of successful cognitive aging, while a less constrained one would not have adequately distinguished those individuals able to maintain extraordinary health as they age. Therefore, with both investigative and public health implications in mind, we hope to have created an ecologically valid definition that advances upon those used in previous studies and will enable a deeper understanding of the predictors of successful cognitive aging, as well as identification of the vulnerable groups and modifiable risk factors to target for intervention.
### Table 4.2.1. Characteristics of Overall Study Sample (N=1,162)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years*</td>
<td>70.3 ± 8.9</td>
</tr>
<tr>
<td>50-59</td>
<td>113 (9.7)</td>
</tr>
<tr>
<td>60-69</td>
<td>456 (39.3)</td>
</tr>
<tr>
<td>70-79</td>
<td>385 (33.1)</td>
</tr>
<tr>
<td>80+</td>
<td>206 (17.8)</td>
</tr>
<tr>
<td>Female</td>
<td>711 (61.2)</td>
</tr>
<tr>
<td>White</td>
<td>157 (13.5)</td>
</tr>
<tr>
<td>Black</td>
<td>186 (16.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>796 (69.9)</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).*
Table 4.2.2. Criteria for Successful Cognitive Aging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease and Disability</td>
<td>565 (48.6)</td>
</tr>
<tr>
<td>No cancer</td>
<td>1076 (92.6)</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>1053 (90.9)</td>
</tr>
<tr>
<td>No cardiac disease</td>
<td>966 (83.1)</td>
</tr>
<tr>
<td>Creatinine clearance rate ≥45 mL/min</td>
<td>957 (82.4)</td>
</tr>
<tr>
<td>Barthel ADL score ≥95</td>
<td>1098 (94.5)</td>
</tr>
<tr>
<td>Cognition</td>
<td>1011 (87.0)</td>
</tr>
<tr>
<td>Baseline MMSE &gt;17 for ≤8 years of education or &gt;23</td>
<td>1112 (95.7)</td>
</tr>
<tr>
<td>for ≥9 years of education</td>
<td></td>
</tr>
<tr>
<td>≤3-point decline on MMSE at follow-up</td>
<td>1037 (89.2)</td>
</tr>
</tbody>
</table>

ADL=Activities of Daily Living; MMSE=Mini-Mental State Examination
Table 4.2.3. Prevalence of Successful Cognitive Aging by Demographic Subgroup*

<table>
<thead>
<tr>
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<th>Successful Cognitive Aging</th>
<th></th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years; mean (SD)</td>
<td>69.8 ± 7.7</td>
<td>70.7 ± 9.6</td>
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<td>0.103</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50-59</td>
<td>34 (30.1)</td>
<td>79 (69.9)</td>
<td></td>
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</tr>
<tr>
<td>60-69</td>
<td>200 (43.9)</td>
<td>256 (56.1)</td>
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<td></td>
</tr>
<tr>
<td>70-79</td>
<td>153 (39.7)</td>
<td>232 (60.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80+</td>
<td>57 (27.7)</td>
<td>149 (72.3)</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>0.0008</td>
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<tr>
<td>Female</td>
<td>238 (33.5)</td>
<td>473 (66.5)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>195 (43.2)</td>
<td>256 (56.8)</td>
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<td></td>
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<td>White</td>
<td>53 (33.8)</td>
<td>104 (66.2)</td>
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<td>Black</td>
<td>72 (38.7)</td>
<td>114 (61.3)</td>
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<td>299 (37.6)</td>
<td>497 (62.4)</td>
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</tbody>
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*Data are given as number (percentage) unless otherwise indicated.
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<th></th>
<th>p-value</th>
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<td></td>
<td>Yes (N=433; 37.3%)</td>
<td>No (N=729; 62.7%)</td>
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<td></td>
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<td>14 (17.5)</td>
<td>66 (82.5)</td>
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<td>0.24</td>
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<td></td>
<td>Male</td>
<td>9 (27.3)</td>
<td>24 (72.7)</td>
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<td>Race/ethnicity</td>
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<td></td>
<td>White</td>
<td>2 (16.7)</td>
<td>10 (83.3)</td>
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<td>Black</td>
<td>4 (36.4)</td>
<td>7 (63.6)</td>
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<tr>
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<td>Hispanic</td>
<td>14 (16.1)</td>
<td>73 (83.9)</td>
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<td>Gender</td>
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<tr>
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<td>Female</td>
<td>106 (40.5)</td>
<td>156 (59.5)</td>
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<tr>
<td></td>
<td>Male</td>
<td>94 (48.5)</td>
<td>100 (51.5)</td>
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<tr>
<td></td>
<td>White</td>
<td>14 (38.9)</td>
<td>22 (61.1)</td>
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<td>21 (38.9)</td>
<td>33 (61.1)</td>
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<tr>
<td></td>
<td>Hispanic</td>
<td>161 (45.5)</td>
<td>193 (54.5)</td>
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<td>70-79</td>
<td>Gender</td>
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<td>82 (36.6)</td>
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<td>71 (44.1)</td>
<td>90 (55.9)</td>
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</tr>
<tr>
<td></td>
<td>White</td>
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<td>37 (61.7)</td>
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<tr>
<td></td>
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<td>29 (46.0)</td>
<td>34 (54.0)</td>
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<tr>
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<td>99 (38.7)</td>
<td>157 (61.3)</td>
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<td>80+</td>
<td>Gender</td>
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<tr>
<td></td>
<td>Female</td>
<td>36 (25.0)</td>
<td>108 (75.0)</td>
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</tr>
<tr>
<td></td>
<td>Male</td>
<td>21 (33.9)</td>
<td>41 (66.1)</td>
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<tr>
<td></td>
<td>White</td>
<td>14 (28.6)</td>
<td>35 (71.4)</td>
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<td></td>
<td>Black</td>
<td>18 (31.6)</td>
<td>39 (68.4)</td>
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<tr>
<td></td>
<td>Hispanic</td>
<td>25 (25.5)</td>
<td>73 (74.5)</td>
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</tbody>
</table>

*Data are given as number (percentage).
5.1 Overview

Older adults shoulder a disproportionate burden of disease and disability: more than 75% of older Americans have at least one chronic illness, and one-fifth are chronically disabled (Federal Interagency Forum on Aging-Related Statistics, 2006; Wolff et al., 2002). As a result, studies of successful aging tend to center on physiological health problems, with less attention paid to the impact of psychosocial factors or how the prevalence of successful aging varies with sociodemographic factors related to the maintenance of good health such as education, literacy, and socioeconomic status.

A higher level of education has been demonstrated to be a strong predictor of cognitive functioning in older age, and may be protective against age-related decline (Elias et al., 1997; Lyketsos et al., 1999). However, reported level of education does not always correlate with reading ability among older adults, so a more direct measurement of literacy may be especially useful in interpreting the results of cognitive screening among low-educated and minority groups; it has even been suggested that reading ability may be a better predictor of memory decline than educational attainment (Albert and Teresi, 1999; Baker et al., 1996; Manly et al., 2003; Weiss et al., 1995). Socioeconomic differences are pervasive in all aspects of health, and there is increasing evidence that environmental effects on biological aging may be responsible for this link (Adams
and White, 2004). A focus on sociodemographic disparities in the prevalence of successful cognitive aging could lead to the implementation of strategies to eliminate these inequalities.

There is a pressing need for intervention studies aimed at the promotion of successful cognitive aging, as the number of older persons wishing to remain active members of society and maintain a high quality of life has dramatically increased (Fries, 1990). Despite the reciprocal nature of the relationship between successful cognitive aging, social connectedness, and quality of life, the latter two are rarely considered in studies of successful aging. Stronger social support, a construct that describes the structure of an individual's social environment and the tangible and emotional resources it provides, has been associated with decreased all-cause mortality, stroke mortality, and cardiovascular disease mortality, as well as with higher functional status (Brummett et al., 2001; House et al., 1988; Michael et al., 1999; Rodriguez et al., 2008). Likewise, self-reported quality of life indicators are highly correlated with objective clinical outcomes and mortality (Han et al., 2009). Because aging is neither a uni-directional nor a uni-dimensional process, we sought to examine how these factors are related to the prevalence of successful cognitive aging, as a better understanding of these relationships will help to further refine its definition.

The key objectives of this study were to (1) examine sociodemographic determinants (education and literacy, health insurance status, and social support) of successful cognitive aging, and (2) differences in quality of life measures in a community-based multi-ethnic cohort of stroke-free older adults.
5.2 Results

5.2.1 Sample Characteristics

The demographic characteristics of the sample with respect to age, gender, and race/ethnicity, are detailed in section 4.2.1. The majority of persons (44%) were married, while 16% were widowed, 16% divorced, 10% separated, and 13% single. The mean number of years of education was 9.5 ± 5.1, with 43% having less than an eighth grade education (95% of whom were Hispanic), 15% having completed high school, and 15% having a college degree or higher. Average score on the WRAT was 43.8 ± 6.7 (maximum 55), and on the WAT was 12.5 ± 6.5 (maximum 30). Of the 965 persons for whom health insurance status was available, 49% were on Medicaid. Sample characteristics are shown in Table 5.2.1.

5.2.2 Prevalence of Successful Cognitive Aging by Level of Education, Literacy, and Socioeconomic Status

The prevalence of successful cognitive aging across sociodemographic subgroups is presented in Table 5.2.2. Neither the number of years nor level of education was significantly different between successful and non-successful cognitive agers; this result did not differ by race or ethnicity. No association was found between literacy and successful cognitive aging among English-speakers, although we did find a marginally significant association among Spanish-
speakers (p=0.053). Of those on Medicaid, a smaller proportion were successfully aging (41% versus 59%; p=0.033).

5.2.3 Comparison of Social Supports in Successful Cognitive Aging

Table 5.2.3 details the prevalence of successful cognitive aging by level of social support. The prevalence of successful cognitive aging differed significantly by marital status (p=0.0006): 40% of single, 38% of married, 28% of widowed, 45% of divorced, and 37% of separated persons were successfully aging. Among the widowed, a significantly smaller amount was classified as successful cognitive agers (28%; p=0.002) as compared to the rest of the sample. A significantly greater proportion of divorced persons, on the other hand, were successfully aging (45%; p=0.020).

There was a significant difference in the prevalence of successful cognitive aging by how many times participants talked to someone on the phone (p=0.005). Of those in the successful cognitive aging group, 65% reported talking to someone on the phone at least once a day or more. The highest prevalence of successful cognitive aging (67%), however, was among those who did not report talking to anyone at all on the phone in the past week. Respondents who said that they had someone to trust and confide in were more likely to be successfully aging than those who did not (38% versus 25%; p=0.026), as were those who almost never felt lonely as compared to individuals who felt lonely sometimes or quite often (41% versus 33%; p=0.022).
Though not of statistical significance, the prevalence estimates of successful cognitive aging were greater among those with three or more friends, those who visited their friends and/or family at least once in the past week, those who reported seeing their friends as often as they wanted to, and those who had someone who would give them any help if they were sick or disabled.

5.2.4 Differences in Quality of Life Measures in Successful Cognitive Aging

Complete data on quality of life were available on 964 of the 1,162 study subjects; these subjects did not differ demographically from the overall sample. Differences in the prevalence of successful cognitive aging by self-reported quality of life are shown in Table 5.2.4. The prevalence of successful cognitive aging was greatest among those reporting a higher quality of life, both for each of the five individual domains of activity (46%; p<0.0001), daily living (46%; p=0.002), health (51%; p<0.0001), support (46%; p=0.012), and outlook (47%; p=0.003), and for total quality of life (mean score 9.57 ± 0.75 versus 9.15 ± 1.16; p<0.0001; maximum score = 10).

5.2.5 Logistic Regression Analyses of Sociodemographic Factors in Successful Cognitive Aging

A multivariate logistic regression model, with the independent variables of age, gender, education, and socioeconomic status, showed that age, gender, and socioeconomic status were strongly inversely associated (i.e., older age, less likely) with the likelihood of successful cognitive aging (advancing age: OR=0.95, 95% C.I. 0.93-0.97, p<0.0001; female: OR=0.73, 95% C.I. 0.55-0.96,
p=0.022; on Medicaid: OR=0.72, 95% C.I. 0.54-0.97; p=0.029). However, when the social support variables of marital status, talking on the phone, having someone to trust, and feeling lonely, and the total quality of life score, were included in the multivariate model with age, gender, education, and socioeconomic status, only the social support variables, quality of life, and age remained significant (Table 5.2.5). Advancing age, being widowed, talking on the phone at least once a week, not having someone to trust, feeling lonely sometimes versus almost never, and reporting a lower quality of life were all associated with a lower odds of successful cognitive aging.

### 5.3 Discussion

The concept of successful cognitive aging is continually evolving, with few of the current models being truly multidimensional (Bowling and Dieppe, 2005). In order to devise appropriate health prevention and promotion interventions, and to accurately measure their utility, the contribution of factors above and beyond those describing disease and disability needs to be elucidated. Importantly, the majority of successful aging definitions put forth by researchers do not include psychosocial measures, yet older adults tend to endorse social engagement and positive outlook over physical health status in qualitative studies about how to best define successful aging (Depp and Jeste, 2006; Knight and Ricciardelli, 2003; Phelan et al., 2004). For this study, we examined several sociodemographic and psychosocial determinants of successful cognitive aging. We described the extent to which the prevalence of successful cognitive aging in
a large cohort of multi-ethnic older adults varies by education, literacy, and socioeconomic status, and how it is associated with social resources and quality of life.

Findings in the literature with respect to educational differences are mixed, but in general do not appear to support a relationship with successful aging (Depp and Jeste, 2006). In this study, we did not find a significant difference in years of education between successful and non-successful cognitive agers. This may be because, by stratifying baseline MMSE cut-offs for cognitive impairment by education in our successful aging definition, we were able to account for the confounding effect of education with cognition and cognitive decline. Scores on the MMSE can be biased by baseline educational level, and in NOMAS, we have previously found that the odds of cognitive decline, defined as in this study by a decrease of at least 3 points on the MMSE from baseline to the time of MRI, were 4.8 times greater (95% C.I. 2.5-8.9) for those with less than eight years of education compared to those with at least eight years (Loring et al., 2010; Wood et al., 2006). The majority of previous studies that have included a measure of cognitive function in their successful aging definition did not use education-adjusted cut-offs, increasing the potential for misclassification among those of non-white race and lower educational level (Anthony et al., 1982; Depp and Jeste, 2006; Fillenbaum et al., 1990; Parker and Philp, 2004). Another potential reason for the lack of association with education in successful cognitive aging studies may be sampling bias, with those older adults with lower education being less likely to participate in such research. This was not a factor in NOMAS: 77%
of the original cohort did not complete high school, and over 42% of the current study sample reported having less than 8 years of education.

With the number of years spent in an educational system not necessarily reflective of the quality of education, particularly among ethnic groups that may not have had equal access to educational opportunities, literacy has emerged as a more quantitative estimation of true educational experience (Lucas et al., 2005; O’Bryant et al., 2007). Importantly, the concept of health literacy has arisen to denote a constellation of skills that constitute one’s ability to perform basic reading and numerical tasks for functioning in the health care environment and acting on health care information (AMA, 1999). However, to our knowledge no prior studies of successful cognitive aging have addressed literacy. While we did not find a significant association between literacy and successful cognitive aging among English-speakers, we did find a marginally significant association among Spanish-speakers, which seems to imply that cultural factors may play a role in the relationship between literacy and successful cognitive aging. Indeed, cultural influences have been found to shape individuals’ attitudes and actions with respect to a variety of health care domains, from physiology and disease etiology, to risk behaviors, intervention and management, to patient-doctor relationships and healthcare decision-making (Berlin and Fowkes, 1983). As low literacy has been associated with substandard medical care and poorer health outcomes, culturally-sensitive interventions to mitigate the impact of low literacy on health and well-being could enhance successful cognitive aging (Berkman et al., 2004).
As we predicted, the prevalence of successful cognitive aging in NOMAS was significantly lower among those with a lower socioeconomic status, as individuals with fewer financial resources tend to experience poorer health (Adler and Ostrove, 1999). Education is often used as a measure of socioeconomic status, as it has been associated with better health practices; in our study, however, health insurance status, which is more directly related to income, but not education, was related to successful cognitive aging, suggesting that greater access to health-promoting resources is a more dominant factor (Galobardes et al., 2006; Mirowsky and Ross, 2003). While some reciprocal influence of socioeconomic status on health is possible, the direct influence of socioeconomic status on health predominates (Haan et al., 1987). More research is needed to determine the role of socioeconomic status throughout the lifespan, particularly in older age, and how the cumulative effect of socioeconomic disadvantage ultimately influences health in later life. And, most studies into successful aging are done on an individual level, yet poverty and inadequate healthcare have been shown to also diminish the health of entire communities (Institute of Medicine, 2003). Clearly, interventions targeting successful cognitive aging should include public health strategies and social and political policies aimed at community improvement, in addition to individual-level risk factor management.

A wealth of research has shown higher levels of social support to be associated with lower cardiovascular morbidity and mortality, and it is thought that social support may exert its influence on health via autonomic pathways and act to buffer the physiologic effects of stress (Boden-Albala et al., 2005; Israel et
al., 2002; Knox and Uvnas-Moberg, 1998; Rodriguez et al., 2008; Seeman and McEwen, 1996). Alternatively, the relationship between low social support and adverse health outcomes may be mediated by physiologic stress, depression, and poorer regulation of vascular risk factors due to decreased engagement in health-promoting behaviors or decreased medication compliance (Boden-Albala et al., 2005). Several social network variables were important in successful cognitive aging in NOMAS. We found significant associations between successful cognitive aging and marital status, number of times spent talking on the telephone, having someone to trust and confide in, and feeling lonely, but not number of friends, number of visits with friends/family, seeing friends/family as often as one would like, or having someone to help if one were sick or disabled. Our finding that a greater prevalence of those who did not report talking to anyone at all on the phone in the past week, compared to those who reported talking on the phone at least once, was unexpected. This may be an artifact of geographical considerations, in that that those who did not report talking to anyone at all on the phone lived closer to relatives and friends, whereas those who reported more times spent talking on the phone lived further, though more examination is warranted. Taken together, our results suggest that having deeper, more connected relationships may be more important than the quantity of relationships and number of social contacts. But, because different situations require different types of support networks, and as the choice of an optimal network depends on the functions it is to perform, more research is warranted to determine exactly which social constructs are most relevant for older adults,
whether they vary by demographics and/or culture, and how they are best measured (Silverstein and Litwak, 1993).

Considering marital status, we found that widowers were significantly less likely to be classified as successful cognitive agers (27.5% of widowers versus 39.7% of others), while divorcees were significantly more likely to be (45.4% of divorcees versus 36.3% of others). Several reasons may explain these findings. As about half of widowers were aged 80 or older, with another almost one-third between 70 and 79 years, poorer health status due to older age could be a confounding factor. Widowhood in and of itself, however, is commonly associated with depression, and is a risk factor for a range of diseases and for immunological dysfunction (Irwin et al., 1987; Prigerson et al., 1997; Umberson et al., 1992). And, recently, those individuals widowed in mid- or later life were found to have a greater than seven-fold increased risk for Alzheimer’s disease compared to married or cohabiting people, with the highest risk found in carriers of the apolipoprotein E\textunderscore{}4 allele (Hakansson et al., 2009). In this sample, a greater percentage of widowed compared to non-widowed persons reported feeling lonely quite often or sometimes (50.8% versus 43.5%; p=0.046). As the maintenance of social interaction and meaningful activities has been demonstrated to be an effective means of mitigating some of the adverse psychological effects of becoming widowed, supportive interventions for persons who have lost a partner may therefore present a promising strategy for encouraging successful cognitive aging (Silverman, 1985). Divorce was more common among younger members of the sample, with 47.5% of divorcees
between the ages of 60 and 69. As discussed in the previous chapter, the prevalence of successful cognitive aging was highest among this age cohort. Marital status has been associated with successful aging in a few studies (e.g., Li et al., 2006), though the evidence is largely inconsistent (Depp and Jeste, 2006). Our finding that the prevalence of successful cognitive aging was higher among divorcees is unexpected given evidence showing an association between divorce and ill-health and mortality (Ikeda et al., 2007; Johnson et al., 2000; Joung et al., 1998). Although, such studies tend to focus on short-term associations with divorce and do not generally consider older adults; a study in England suggests that divorce is not associated with any long-term effects on health (Solomou et al., 1998).

Chronic disease, disability, and cognitive difficulties can negatively affect quality of life, so we hypothesized that quality of life would be associated with successful cognitive aging (Desai et al., 2010; Walker, 2007). As expected, all domains of our quality of life index – activity, daily living, health, support, and outlook – as well as the total quality of life index score were significantly associated with successful cognitive aging. Together with our findings on social resources, these results lend support to the active engagement hypothesis of successful cognitive aging, which involves both being connected to other persons and engaging in productive activities (Rowe and Kahn, 1998). Indeed, multivariate logistic regression showed that in NOMAS, social resources and quality of life appear to be more important predictors of successful cognitive aging than demographic variables alone.
5.4 Limitations

The use of a community-based multi-ethnic sample gave us the ability to study a representative range of several sociodemographic and psychosocial characteristics of older adults, although there are several limitations to our study that are worth noting. This sample may have been biased due to a survivor effect, as the MRI sub-study cohort is somewhat healthier than the overall prospective cohort; however, this would likely cause an underestimation of the associations found. Social resources and quality of life were only assessed at one time point, so we do not know how they have changed over time, either up until and/or following their measurement. Reverse causality has been proposed as an issue with respect to social supports and quality of life, which are more often considered a causal factor in successful cognitive aging, but may just as well be dependent on successful cognitive aging (House et al., 1988).

Our quality of life index and social resources questionnaire are fairly short and capture only some of the many psychological and physical manifestations of these broad concepts; for example, we do not have specific data on participation in community-based organizations or religious activities. Though subjective, these measures may better reflect the intensely personal and interpretable concept of successful cognitive aging as they represent individuals’ points of view.

While our assessment of education and literacy, socioeconomic status, social resources and quality of life is certainly not all-inclusive, it does stress the
need for the consideration of non-medical factors in assessments of successful cognitive aging, and encourages a paradigm shift in successful aging research from largely biomedical to more biopsychosocial. The components of successful cognitive aging are interdependent and synergistic, in that avoiding disease and disability makes it easier to maintain social integration, a good quality of life, and better cognitive health, and vice versa (Silverstein and Parker, 2002).
Table 5.2.1. Characteristics of Study Sample (N=1,162)

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>155 (13.3)</td>
</tr>
<tr>
<td>Married</td>
<td>506 (43.5)</td>
</tr>
<tr>
<td>Widowed</td>
<td>189 (16.3)</td>
</tr>
<tr>
<td>Divorced</td>
<td>183 (15.7)</td>
</tr>
<tr>
<td>Separated</td>
<td>115 (9.9)</td>
</tr>
<tr>
<td>Education, years*</td>
<td>9.5 ± 5.1</td>
</tr>
<tr>
<td>Eighth grade or less</td>
<td>493 (42.5)</td>
</tr>
<tr>
<td>Some high school</td>
<td>162 (13.9)</td>
</tr>
<tr>
<td>Completed high school</td>
<td>175 (15.1)</td>
</tr>
<tr>
<td>Some college</td>
<td>156 (13.4)</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>175 (15.1)</td>
</tr>
<tr>
<td>Literacy score*</td>
<td></td>
</tr>
<tr>
<td>WRAT</td>
<td>43.8 ± 6.7</td>
</tr>
<tr>
<td>WAT</td>
<td>12.5 ± 6.5</td>
</tr>
<tr>
<td>On Medicaid*</td>
<td>469 (48.6)</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).
* N=965.
Table 5.2.2. Prevalence of Successful Cognitive Aging by Demographic Subgroup*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Successful Cognitive Aging</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (N=433; 37.3%)</td>
<td>No (N=729; 62.7%)</td>
<td></td>
</tr>
<tr>
<td>Education, years; mean (SD)</td>
<td>9.8 ± 5.0</td>
<td>9.3 ± 5.1</td>
<td>0.139</td>
</tr>
<tr>
<td>Eighth grade or less</td>
<td>170 (34.5)</td>
<td>323 (65.5)</td>
<td>0.092</td>
</tr>
<tr>
<td>Some high school</td>
<td>65 (40.1)</td>
<td>97 (59.9)</td>
<td>0.417</td>
</tr>
<tr>
<td>Completed high school</td>
<td>70 (40.0)</td>
<td>105 (60.0)</td>
<td>0.417</td>
</tr>
<tr>
<td>Some college</td>
<td>59 (37.8)</td>
<td>97 (62.2)</td>
<td>0.877</td>
</tr>
<tr>
<td>College graduate or more</td>
<td>69 (39.4)</td>
<td>106 (60.6)</td>
<td>0.520</td>
</tr>
<tr>
<td>Literacy score; mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRAT</td>
<td>44.1 ± 6.2</td>
<td>43.6 ± 7.0</td>
<td>0.517</td>
</tr>
<tr>
<td>WAT</td>
<td>13.1 ± 6.5</td>
<td>12.1 ± 6.4</td>
<td>0.053</td>
</tr>
<tr>
<td>On Medicaid*</td>
<td>194 (41.4)</td>
<td>275 (58.6)</td>
<td><strong>0.033</strong></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.
WRAT=Wide Range Achievement Test; WAT=Word Accentuation Test
*N=965.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Successful Cognitive Aging (N=1,162)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>62 (40.0)</td>
<td>0.529*</td>
</tr>
<tr>
<td>Married</td>
<td>193 (38.1)</td>
<td>0.792</td>
</tr>
<tr>
<td>Widowed</td>
<td>52 (27.5)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Divorced</td>
<td>83 (45.4)</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td>Separated</td>
<td>43 (37.4)</td>
<td>0.939</td>
</tr>
<tr>
<td>Number of friends</td>
<td></td>
<td>0.365</td>
</tr>
<tr>
<td>None</td>
<td>10 (30.3)</td>
<td></td>
</tr>
<tr>
<td>One or two</td>
<td>34 (30.6)</td>
<td></td>
</tr>
<tr>
<td>Three or four</td>
<td>89 (37.9)</td>
<td></td>
</tr>
<tr>
<td>Five or more</td>
<td>300 (38.3)</td>
<td></td>
</tr>
<tr>
<td>Talking on the telephone</td>
<td></td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>Not at all</td>
<td>16 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Once per week</td>
<td>26 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Two to six times per week</td>
<td>110 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Once a day or more</td>
<td>281 (38.8)</td>
<td></td>
</tr>
<tr>
<td>Number of visits with friends/family</td>
<td></td>
<td>0.912</td>
</tr>
<tr>
<td>Not at all</td>
<td>78 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Once per week</td>
<td>102 (37.2)</td>
<td></td>
</tr>
<tr>
<td>Two to six times per week</td>
<td>176 (38.2)</td>
<td></td>
</tr>
<tr>
<td>Once a day or more</td>
<td>77 (37.4)</td>
<td></td>
</tr>
<tr>
<td>Having someone to trust</td>
<td></td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td>No</td>
<td>18 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>415 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Feeling lonely</td>
<td></td>
<td><strong>0.022</strong></td>
</tr>
<tr>
<td>Quite often</td>
<td>51 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>119 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Almost never</td>
<td>263 (40.8)</td>
<td></td>
</tr>
<tr>
<td>Seeing friends/family as often as one</td>
<td></td>
<td>0.288</td>
</tr>
<tr>
<td>not as often as wants to</td>
<td>161 (35.4)</td>
<td></td>
</tr>
<tr>
<td>As often as wants to</td>
<td>272 (38.5)</td>
<td></td>
</tr>
<tr>
<td>Having someone to help</td>
<td></td>
<td>0.294</td>
</tr>
<tr>
<td>No one willing or able to help</td>
<td>53 (33.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>380 (37.9)</td>
<td></td>
</tr>
</tbody>
</table>

* Reference group is all other marital subgroups (e.g., persons who were single vs. those who were married, widowed, divorced, or separated).
### Table 5.2.4. Differences in Quality of Life Measures

<table>
<thead>
<tr>
<th>Quality of Life Index</th>
<th>Successful Cognitive Aging (N=964)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Activity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Highest)</td>
<td>429 (46.2)</td>
<td>499 (53.8)</td>
</tr>
<tr>
<td>1</td>
<td>4 (14.3)</td>
<td>24 (85.7)</td>
</tr>
<tr>
<td>0</td>
<td>0 (0.0)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Daily Living score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>432 (45.6)</td>
<td>515 (54.4)</td>
</tr>
<tr>
<td>1</td>
<td>1 (7.1)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>0</td>
<td>0 (0.0)</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>Health score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>324 (50.7)</td>
<td>315 (49.3)</td>
</tr>
<tr>
<td>1</td>
<td>106 (34.3)</td>
<td>203 (65.7)</td>
</tr>
<tr>
<td>0</td>
<td>3 (17.6)</td>
<td>14 (82.3)</td>
</tr>
<tr>
<td>Support score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>422 (46.0)</td>
<td>496 (54.0)</td>
</tr>
<tr>
<td>1</td>
<td>9 (25.7)</td>
<td>26 (74.3)</td>
</tr>
<tr>
<td>0</td>
<td>2 (18.2)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>Outlook score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>380 (47.3)</td>
<td>423 (52.7)</td>
</tr>
<tr>
<td>1</td>
<td>50 (33.3)</td>
<td>100 (66.7)</td>
</tr>
<tr>
<td>0</td>
<td>3 (27.3)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Total Quality of Life Score*</td>
<td>9.57 ± 0.75</td>
<td>9.15 ± 1.16</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).

* Fisher’s exact test.
Table 5.2.5. Odds of Successful Cognitive Aging by Sociodemographic Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted Odds Ratio* (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.95 (0.93-0.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>0.90 (0.66-1.22)</td>
<td>0.488</td>
</tr>
<tr>
<td>Years of education</td>
<td>1.02 (0.99-1.05)</td>
<td>0.247</td>
</tr>
<tr>
<td>On Medicaid</td>
<td>0.85 (0.63-1.16)</td>
<td>0.304</td>
</tr>
<tr>
<td>Widowed</td>
<td>0.65 (0.42-0.97)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Divorced</td>
<td>1.01 (0.70-1.47)</td>
<td>0.936*</td>
</tr>
<tr>
<td>Talking on the telephone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once a day or more</td>
<td>0.13 (0.03-0.49)</td>
<td>0.002</td>
</tr>
<tr>
<td>Two to six times per week</td>
<td>0.12 (0.03-0.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Once per week</td>
<td>0.13 (0.03-0.53)</td>
<td>0.005</td>
</tr>
<tr>
<td>Not at all</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Having someone to trust</td>
<td>1.93 (1.01-3.69)</td>
<td>0.045</td>
</tr>
<tr>
<td>Feeling lonely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quite often</td>
<td>0.87 (0.57-1.37)</td>
<td>0.552</td>
</tr>
<tr>
<td>Sometimes</td>
<td>0.70 (0.51-0.95)</td>
<td>0.025</td>
</tr>
<tr>
<td>Almost never</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Total Quality of Life Score</td>
<td>1.56 (1.31-1.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for all other sociodemographic characteristics and length of time between baseline and MRI.

* Reference group is all other marital subgroups.
6.1 Overview

Though there is no universally accepted definition of successful cognitive aging, nearly all of those currently in use involve aging without the development of major life-threatening chronic diseases. Cardiovascular diseases are the primary cause of death in older adults, and there is an abundance of epidemiological and pathological evidence showing that vascular disease contributes to cognitive impairment (Barone et al., 2009; Beeri et al., 2009; Heron et al., 2009; Rojas-Fernandez and Moorhouse, 2009). Likewise, studies have shown that those who survive into old age tend to have lower levels of risk factors for common chronic diseases, particularly cardiovascular disease (Burke et al., 2001; Seeman et al., 1994). Consistent predictors of healthy aging in the Honolulu-Asia Aging Study, for example, were low blood pressure, low serum glucose, not smoking cigarettes, and not being obese (Reed et al., 1998).

More recently, those factors identified as major determinants of cardiovascular disease – namely, age, hypertension, hyperlipidemia, diabetes, and smoking – have been codified into risk models to more effectively assess cardiovascular risk (Wood et al., 1998; Wilson et al., 1998). In providing improved risk stratification, such models allow for more precise targeting of preventive therapies; for instance, according to current United States treatment guidelines, lipid-lowering statin therapy is considered an option for individuals with 10-year
risk estimates of 10% of higher (Grundy et al., 2004). Vascular risk models are powerful in their simultaneous consideration of established, independent, biologically relevant risk factors, and have been improved of late with the addition of more novel markers, such as homocysteine, C-reactive protein, and hemoglobin A1c, and behavioral and anthropometric measures (Ridker et al., 2007; Sacco et al., 2009; Wilson et al., 1998). The NOMAS Global Vascular Risk Score (refer to section 3.3.5 for a detailed description) was designed to predict the global vascular risk of MI, stroke, or vascular death in multi-ethnic individuals. The 10-year event-free probabilities associated with the NOMAS GVRS have been previously estimated as 0.95 for the first quartile of GVRS, 0.89 for the second quartile, 0.79 for the third quartile, and 0.56 for the fourth quartile (Sacco et al., 2009). The NOMAS GVRS has also been associated with cognitive performance (Loring et al., 2010). Similarly, the Framingham Stroke Risk Profile as well has been associated with performance decrements in multiple cognitive domains (Elias et al., 2004). The effect of global vascular risk on successful cognitive aging, however, has not been described.

Vascular disease, which includes a range of conditions affecting the circulatory system, is so strongly age-associated that it has been proposed as a biomarker of aging, but it is not an obligatory finding in all aged populations; while vascular disease may accelerate physical, functional, and cognitive declines found along with advancing age, it does not account for them entirely (Grundy, 1999; Marmot, 1992; Newman et al., 2003; Simons et al., 1992). Depressive symptoms are often comorbid with vascular disease and its risk factors, and
vascular depression has been proposed as a clinical subtype of major
depression in later life (Alexopoulos et al., 1997). There is some evidence
suggesting that depression may be a risk factor for cognitive decline, but this
remains controversial as there are few prospective studies with a sufficiently long
follow-up period (Jorm, 2000).

The postulated link between depression and cognition has been explained
by some authors to be due to common cerebrovascular pathology, though it may
be more likely that the comorbid presence of cerebrovascular pathology in
depression does not mediate, but rather amplifies, the process of cognitive
decline (Alexopoulos et al., 1997; Chen et al., 1999; Ng et al., 2009; Thomas et
al., 2002). Depression is the leading global cause of years of health lost to
disease in both men and women; currently the fourth leading contributor to the
global burden of disease, by 2020, it is projected to become the first (WHO,
2008). Depressive symptoms are common among older adults, and even
symptoms of mild severity are associated with an increased disability burden
(Barry et al., 2009). Depression may affect motivation, leading to reduced health-
seeking behaviors and physical inactivity (Armenian et al., 1998). Additionally,
depression is associated with psychological stress that is thought to increase
disease susceptibility through alterations in neural, hormonal, and immunological
functioning (Turner and Noh, 1988). A recent meta-analysis showed that, based
on the results of the only seven studies conducted to date that have analyzed the
relationship between successful aging and psychosocial variables, moderate
support has been found for the absence of depression, warranting further research (Depp and Jeste, 2006).

Although aging is ultimately unavoidable, its course may be modified (Christensen et al., 2009). As a result, the evaluation of those risk factors that are modifiable, and of which prevention and/or treatment may promote successful cognitive aging, is a critical area of research. The key objectives of this study were to examine (1) the association between the NOMAS global vascular risk score and successful cognitive aging, and (2) the association between depressive symptoms and successful cognitive aging, adjusting for sociodemographic and vascular risk factors.

6.2 Results

6.2.1 Sample Characteristics

The demographic characteristics of the sample with respect to age, gender, and race/ethnicity, are detailed in section 4.2.1, and education and socioeconomic status in section 5.2.1. Mean GVRS score was 8.6 ± 0.9. The prevalence of clinically significant depression (CES-D score ≥16) was 17%, with a mean CES-D score of 8.3 ± 9.4. For the 965 participants for whom baseline HDRS scores were available, the mean score was 3.1 ± 3.8. The proportion of persons reporting antidepressant use was 7%. Sample characteristics are displayed in Table 6.2.1.
6.2.2 Global Vascular Risk Score and Successful Cognitive Aging

Results of logistic regression analyses comparing the odds of successful cognitive aging for categories of GVRS, adjusted for length of time between baseline and MRI, are shown in Table 6.2.2. For each additional point on the GVRS, the odds of being in the successful cognitive aging group were 28% lower (OR=0.72, 95% C.I. 0.62-0.85; p<0.0001). After further adjustment for level of education and socioeconomic status, the odds of being in the successful cognitive aging group were 36% lower for each additional point on the GVRS (OR=0.64, 95% C.I. 0.54-0.76; p<0.0001). Compared to the highest quartile of GVRS, the odds of successful cognitive aging were 1.5 times greater for the third quartile of GVRS (OR=1.50, 95% C.I. 1.03-2.19; p=0.034), 1.6 times greater for the second quartile (OR=1.63, 95% C.I. 1.12-2.36; p=0.010), and more than three-fold greater for the lowest quartile of GVRS (OR=3.25, 95% C.I. 2.13-5.46; p<0.0001).

6.2.3 Depressive Symptoms and Successful Cognitive Aging

The prevalence of clinically significant depression (CES-D score ≥16) was 17%. Those with a CES-D score ≥16 were more likely to be female (73% vs. 59%; p=0.0001), non-white (91% vs. 86% of all others; p=0.0318), Hispanic (76% vs. 69% for all others; p=0.039), and less educated (8.8 years vs. 9.6 years; 0.029), to use antidepressants (15% vs. 5%; p<0.0001), and to have a higher HDRS score at baseline (5.7 vs. 2.6; p<0.0001) (Table 6.2.3).
Results of logistic regression analyses comparing the odds of successful cognitive aging for categories of CES-D score, adjusted for GVRS, years of education, socioeconomic status, antidepressant use, and length of time between baseline and MRI, are shown in Table 6.2.4. The odds of being in the successful cognitive aging group were 1.64 times greater for those with a CES-D score <16 than for those with a CES-D score above this cut-off (OR=1.64, 95% C.I. 1.07-2.51; p=0.024). Modeling the CES-D as a continuous variable, for every unit increase in CES-D score, the odds of successful cognitive aging decreased by 2% (OR=0.98, 95% C.I. 0.96-1.00; p=0.021), and compared to the highest quintile of CES-D score, the odds of successful cognitive aging were over 1.7 times greater for the lowest quintile (OR=1.74, 95% C.I. 1.08-2.79; p=0.022).

Results of logistic regression analyses comparing the odds of successful cognitive aging by duration of depressive symptomatology, adjusted for GVRS, years of education, socioeconomic status, antidepressant use, and length of time between baseline and MRI, are shown in Table 6.2.5. Persons who were depressed at baseline had a 73% lower odds of successful cognitive aging compared to those who were not depressed at baseline or follow-up (OR=0.27, 95% C.I. 0.10-0.72; p=0.009), while those who were depressed at both baseline and follow-up had a 78% lower odds of successful cognitive aging (OR=0.22, 95% C.I. 0.08-0.61; p=0.004). Those who were depressed at follow-up but not at baseline did not have significantly different odds of successful cognitive aging versus those who were not depressed at either time point.
6.3 Discussion

Central to successful aging is a protective vascular risk factor profile, yet while studies strongly support an association between the presence of vascular risk factors and a lower likelihood of successful cognitive aging, little is known about the effect of global vascular risk (Depp and Jeste, 2006; Gorelick, 2005). The NOMAS global vascular risk score predicts the overall combined risk of adverse vascular outcomes, and therefore represents a more comprehensive determinant of successful cognitive aging (Sacco et al., 2009). Consistent with our hypothesis, we not only found that the odds of successful cognitive aging decreases by almost one-third for every unit increase in GVRS, but we also observed a dose-response for increasing quartiles of GVRS.

The clustering of vascular risk factors in an individual is strongly associated with cardiovascular events and cardiovascular mortality, and increases with age, limiting longevity (Anderson et al., 1991; Chang et al., 2001; Criqui et al., 1980; Greenlund et al., 2004; Yusuf et al., 1998). As well, individuals with clusters of cardiovascular risk factors have a significantly lower health-related quality of life, independent of sociodemographic characteristics and other comorbidities, and are at least 40% less likely to be employed, whereas a beneficial cardiovascular risk profile is related to greater societal productivity and lower Medicare costs in later years (Sullivan et al., 2008; Sullivan and Ghushchyan, 2007; Daviglus et al., 1998). More than one-quarter of American adults have multiple risk factors for heart disease and stroke, while the percentage of adults with no risk factors, and as well the proportion that engage
in healthy lifestyles, on the other hand, is very low (CDC, 2001; Ford et al., 2001; Greenlund et al., 2004). Moreover, the prevalence of cardiovascular disease is expected to continue to rise as a result of dramatic increases in obesity, diabetes, hypertension, and hyperlipidemia: current estimates suggest that 44 million adults in the United States are obese, almost 11 million have diabetes, 50 million are hypertensive, and 42 million have high blood cholesterol levels (Bonow et al., 2002; National Center for Health Statistics, 2001; AHA, 2002). Clustering of cardiovascular risk is associated not only with physical disease and disability, but also with cognitive health. For instance, participants of the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study who were obese and had high systolic blood pressure and total cholesterol had six times the risk of dementia when compared to those with no risk factors (Kivipelto et al., 2005). And, perhaps the most well known cluster of cardiovascular risk factors, the metabolic syndrome, is also a risk factor for accelerated cognitive aging (Yaffe, 2007).

This is the first study, to our knowledge, however, to examine the relationship between global vascular risk and successful cognitive aging. With early detection of at-risk persons crucial to the success of medical management and behavioral interventions, risk assessment tools such as the GVRS, which take into account multiple sociodemographic and cardiovascular risk factors simultaneously, may be a more effective means for guiding comprehensive prevention efforts and increasing the opportunity for successful cognitive aging.
The prevalence of clinically significant depression (CES-D score ≥16) in this sample was 17%, which is comparable to estimates reported in other large cohort studies (Schulz et al., 2000). Age trends for depressive symptoms captured by self-report scales such as the CES-D show a curvilinear pattern, with the highest scores found in the youngest (20-29 years) and oldest (75 years and above) age groups (Fiske, Gatz & Pedersen, 2003; Newmann, 1989). And, the prevalence, presentation, risk factors, treatment strategies, and outcomes of depression differ with advancing age (Karel, 1997). To our knowledge, this is the first study to look at the impact of incremental changes in depressive symptoms on successful cognitive aging, as well as at the duration of depressive symptoms. Given that our successful cognitive aging definition precludes disease and disability, and that disease and disability are both strong predictors of depression in older adults, we correctly hypothesized that depressive symptomatology would be associated with a lower likelihood of successful cognitive aging in our study (Roberts et al., 1997). We found that those who did not meet criteria for clinical depression had a 64% greater odds of successful cognitive aging, and that the odds of successful cognitive aging were 2% lower for every one-point increase in CES-D score, though we were not able to show a dose response.

Mild to moderate levels of depressive symptoms have recently been associated with worse self-rated successful aging, poorer physical and emotional functioning, lower optimism, more negative attitudes toward aging, lower personal mastery and self-efficacy, and greater anxiety and hostility (Vahia et al., 2010). Our finding that persons who reported symptoms consistent with
depression at both baseline and at follow-up had a much lower likelihood of successful cognitive aging has important implications for intervention. The response to therapy and eventual outcome for common psychological disorders such as depression are inversely related to their chronicity, irrespective of treatment type, so prompt symptom recognition by healthcare providers is critical (Mynors-Wallis and Gath, 1997; Seivewright et al., 1998).

Interestingly, GVRS was not associated with depressive symptoms, whether considered categorically (CES-D<16 vs. CES-D≥16) or continuously (CES-D score). Though itself associated with successful cognitive aging, GVRS did not appear to mediate the relationship between depressive symptoms and successful cognitive aging, suggesting that depression may influence successful cognitive aging through different pathways. For instance, evidence of hyperactivity of the hypothalamic-pituitary-adrenal axis in depressed patients has led to the theory that the neurotoxic effects of centrally-mediated overproduction of corticotropin releasing hormone, and/or excessive activity of inflammatory cytokines, may mediate depressive symptoms through damage to or destruction of hippocampal cells or via the suppression of neurogenesis (Gillespie and Nemeroff, 2005). As well, because hypothalamic-pituitary-adrenal axis dysregulation is related to many cardiovascular disease risk factors (including truncal obesity, hypercholesterolemia, hypertriglyceridemia, and hypertension), adequate treatment of depression may promote successful cognitive aging from a variety of angles (Agabiti-Rosei et al., 1983; Rosmond and Bjorntorp, 2000). Physical, cognitive, and emotional health are all key components of successful
cognitive aging, so multidisciplinary approaches to the care of depressed older persons that integrate medical and psychiatric care are needed (Bartels et al., 2004; Unutzer et al., 2002).

6.4 Limitations

There are several potential limitations to this study that are worth noting. The NOMAS GVRS has not been validated in other cohorts, though a major strength is that it is applicable to non-white subjects. Data on depression was captured using two different instruments: at baseline with the HDRS, and at the time of MRI with the CES-D. However, the efficacies (area under the receiver operating characteristic curve, AUC) of the CES-D and HDRS as screening instruments are comparable, and the CES-D has been found to be tightly correlated with various versions of the Hamilton form (Caracciolo and Giaquinto, 2002; Lewisohn, 1997).

The CES-D does not provide criteria for the diagnosis of clinical depression; however, the scale does allow for the assessment of symptom severity, particularly within the 8-20% percent of individuals who may have subsyndromal depression (Blazer, 2003). And, there is a potential for self-report depression scales to overestimate rates of depressive symptoms among older populations through endorsement of somatic symptoms that may be related to physical illness or frailty rather than depression (Fonda & Herzog, 2001). The CES-D, though, contains fewer somatic items relative to other scales such as the Beck Depression Inventory and Zung Self-Rating Depression Scale, and the
CES-D somatic and retarded activity factor is strongly correlated with the depressed affect factor, so it is likely that higher CES-D scores in older adults more accurately reflect depression rather than physical illness (Davidson et al., 1994; Gatz and Hurwicz, 1990; Hertzog et al., 1990). Additionally, while we were able to adjust for antidepressant medication use, we did not evaluate type, dosage, duration of, or adherence to treatment.

Application of existing treatments for cardiovascular risk reduction and management of depression, coupled with primary prevention efforts, could potentially modify the course of cognitive aging (Fillit et al., 2008). Our results stress the importance of considering the range of these factors – depressive symptoms and duration versus depressed or not, and global vascular risk instead of isolated cardiovascular risk factors – given that even moderate increases in risk are met with substantial decreases in the likelihood of successful cognitive aging.
Table 6.2.1. Characteristics of Study Sample (N=1,162)

<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D score*</td>
<td>8.3 ± 9.4</td>
</tr>
<tr>
<td>≥16</td>
<td>195 (16.8)</td>
</tr>
<tr>
<td>Quintile 1 (&lt;1)</td>
<td>281 (24.2)</td>
</tr>
<tr>
<td>Quintile 2 (1-2)</td>
<td>152 (13.1)</td>
</tr>
<tr>
<td>Quintile 3 (3-6)</td>
<td>267 (23.0)</td>
</tr>
<tr>
<td>Quintile 4 (7-13)</td>
<td>224 (19.3)</td>
</tr>
<tr>
<td>Quintile 5 (14+)</td>
<td>238 (20.5)</td>
</tr>
<tr>
<td>Baseline HDRS*</td>
<td>3.1 ± 3.8</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>52 (7.2)</td>
</tr>
<tr>
<td>GVRS*</td>
<td>8.6 ± 0.9</td>
</tr>
<tr>
<td>Quartile 1 (&lt;8.0)</td>
<td>262 (24.7)</td>
</tr>
<tr>
<td>Quartile 2 (8.0-8.7)</td>
<td>285 (26.9)</td>
</tr>
<tr>
<td>Quartile 3 (8.7-9.3)</td>
<td>249 (23.5)</td>
</tr>
<tr>
<td>Quartile 4 (9.3+)</td>
<td>264 (24.9)</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).
* N=965.

CES-D=Center for Epidemiologic Studies Depression Scale; HDRS=Hamilton Depression Index total score; GVRS=Global Vascular Risk Score
Table 6.2.2. Odds of Successful Cognitive Aging by Global Vascular Risk Score

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio(^+) (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>GVRS, continuous scale</td>
<td>0.72 (0.62-0.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GVRS, quartiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (&lt;8.0)</td>
<td>2.51 (1.68-3.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Quartile 2 (8.0-8.7)</td>
<td>1.92 (1.32-2.78)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Quartile 3 (8.7-9.3)</td>
<td>1.57 (1.11-2.35)</td>
<td>0.012</td>
</tr>
<tr>
<td>Quartile 4 (9.3+)</td>
<td>reference</td>
<td></td>
</tr>
</tbody>
</table>

\(^{+}\)Odds ratios are adjusted for length of time between baseline and MRI.

\(^{\hat{\cdot}}\)Odds ratios are adjusted for years of education, socioeconomic status, and length of time between baseline and MRI.
Table 6.2.3. Characteristics of Study Sample by CES-D Depressive Symptom Category*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CES-D Score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;16</td>
<td>≥16</td>
</tr>
<tr>
<td>Age, years; mean (SD)</td>
<td>70.4 ± 8.8</td>
<td>69.9 ± 9.4</td>
</tr>
<tr>
<td>Female</td>
<td>568 (58.7)</td>
<td>143 (73.3)</td>
</tr>
<tr>
<td>White</td>
<td>140 (14.5)</td>
<td>17 (8.7)</td>
</tr>
<tr>
<td>Black</td>
<td>158 (16.6)</td>
<td>28 (14.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>652 (68.6)</td>
<td>144 (76.2)</td>
</tr>
<tr>
<td>Education, years; mean (SD)</td>
<td>9.6 ± 5.1</td>
<td>8.8 ± 5.0</td>
</tr>
<tr>
<td>On Medicaid</td>
<td>377 (47.4)</td>
<td>92 (54.4)</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>31 (5.3)</td>
<td>21 (15.2)</td>
</tr>
<tr>
<td>Baseline HDRS; mean (SD)</td>
<td>2.6 ± 3.3</td>
<td>5.7 ± 4.9</td>
</tr>
<tr>
<td>GVRS; mean (SD)</td>
<td>8.6 ± 0.9</td>
<td>8.7 ± 0.9</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.

* Fisher’s exact test.
Table 6.2.4. Odds of Successful Cognitive Aging by CES-D Depressive Symptom Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted Odds Ratio* (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D, continuous symptom scale</td>
<td>0.98 (0.96-1.00)</td>
<td>0.021</td>
</tr>
<tr>
<td>CES-D, dichotomous cut-off for clinical depression (&lt;16 vs. ≥16)</td>
<td>1.64 (1.07-2.51)</td>
<td>0.024</td>
</tr>
<tr>
<td>CES-D, quintiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1 (&lt;1)</td>
<td>1.74 (1.08-2.79)</td>
<td>0.022</td>
</tr>
<tr>
<td>Quintile 2 (1-2)</td>
<td>1.48 (0.84-2.62)</td>
<td>0.178</td>
</tr>
<tr>
<td>Quintile 3 (3-6)</td>
<td>0.94 (0.58-1.52)</td>
<td>0.803</td>
</tr>
<tr>
<td>Quintile 4 (7-13)</td>
<td>1.42 (0.88-2.31)</td>
<td>0.154</td>
</tr>
<tr>
<td>Quintile 5 (14+)</td>
<td><em>reference</em></td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for NOMAS Global Vascular Risk Score, years of education, socioeconomic status, antidepressant use, and length of time between baseline and MRI.
### Table 6.2.5. Odds of Successful Cognitive Aging by Duration of Depressive Symptoms (N=965)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio* (95% C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed at baseline only</td>
<td>0.27 (0.10-0.72)</td>
<td>0.009</td>
</tr>
<tr>
<td>Depressed at follow-up only</td>
<td>0.70 (0.44-1.11)</td>
<td>0.133</td>
</tr>
<tr>
<td>Depressed at baseline and follow-up</td>
<td>0.22 (0.08-0.61)</td>
<td>0.004</td>
</tr>
<tr>
<td>Not depressed at baseline or follow-up</td>
<td>reference</td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratios are adjusted for NOMAS Global Vascular Risk Score, years of education, socioeconomic status, antidepressant use, and length of time between baseline and MRI.
Chapter VII. Subclinical Vascular Brain Damage as a Correlate of Successful Cognitive Aging

7.1 Overview

White matter hyperintensities are areas of increased signal often found incidentally on Flair/T2-weighted MRI scans of the brains of clinically asymptomatic individuals, and are attributed to breakdown of the blood-brain barrier (Wright et al., 2008). Age is the strongest predictor of WMH, but cerebrovascular risk factors including hypertension, carotid atherosclerosis, history of transient ischemic attack, collagenous thickening of cerebral veins, decreased cortical blood vessel density, and markers of small vessel disease in the circulation have also been related to a greater load of WMH (de Leeuw et al., 2001; Markus et al., 2005; Moody et al., 2004; Pico et al., 2002). The underlying etiology of WMH is controversial, though ischemic small vessel disease has been implicated as a causal factor because WMH correspond to vascular disease and microangiopathy in vivo and in pathological studies, and are more common in individuals with vascular risk factors (Fazekas et al., 1993; Jeerakathil et al., 2004). Other reasons for WMH formation put forth include myelin pallor, gliosis, atrophy of the neuropil, and breakdown of the subependymal ventricular lining (de Leeuw et al., 2001; Longstreth et al., 1996; Pantoni et al., 1996; Sabri et al., 1999; Scheltens et al., 1992).

WMH tend to form in the frontal regions of the brain, and with increasing age and co-occurrence of cardiovascular risk factors, progressively advance
more posteriorly (Artero et al., 2004). Theorized to represent injury to the brain parenchyma and disruption of neural circuitry, WMH are associated with cognitive impairment, mood dysregulation and neuropsychiatric deficits, motor dysfunction and gait disturbances, medical comorbidities, and a poor prognosis in terms of stroke, myocardial infarction, and death (Fazekas et al., 1988; Longstreth et al., 1996; Pantoni and Inzitari, 1998; Whitman, 2001; Ylikoski et al., 1995). However, though progress has been made in understanding the pathogenesis and clinical implications of white matter hyperintensities, their effect on successful cognitive aging has not been investigated.

Neuropathological studies have demonstrated that there is little neuron loss in normal aging, but imaging data reveal differences in regional and global brain volume (Courchesne et al., 2000; Morrison and Hof, 1997). The aforementioned factors associated with the presence of WMH are also associated with indices of brain atrophy (Manolio et al., 1994). Advancing age has been associated in a large number of studies with increased ventricular volume and decreased cerebral hemispheric volume, the mechanism of which may be declining cerebral perfusion (Coffey et al., 1992; Laffey et al., 1984; Resnick et al., 2003; Takeda et al., 1988). Overall cardiovascular risk profile and subclinical atherosclerosis are correlated with brain atrophy as well, suggesting a vascular basis for the decreased blood flow in the pathogenesis of these cerebral changes (Carmelli et al., 1999; Manolio et al., 1999; Melamed et al., 1980; Soininen et al., 1992; Swan et al., 1998; Wong et al., 2003). Brain atrophy has functional consequences in terms of decreased cognitive performance in the
absence of dementia or clinical stroke, with deficits noted in executive
functioning, visuospatial skills, attention, and memory, and which become more
pronounced in the setting of greater cardiovascular risk (Longstreth et al., 2000;
Seshadri et al., 2004; Schmidt et al., 1995; Soderland et al., 2004). Even
relatively subtle increases in brain atrophy have cognitive consequences,
particularly in those regions responsible for executive functioning (Swan et al.,
2000). While most older adults show some brain tissue loss over time, the trend
toward less volume loss in healthier samples suggests that degree of brain
atrophy may be related to successful cognitive aging (Resnick et al., 2003).

Up to one-third of older adults without clinically recognized stroke have
radiologic or pathologic evidence of cerebral infarction (Longstreth et al., 1998;
Price et al., 1997; Schneider et al., 2004; Vermeer et al., 2002). These subclinical
infarcts can result in or lower the threshold for dementia, have a synergistic effect
with Alzheimer disease pathology, and may add to cognitive impairment
(Schneider et al., 2004; Snowdon et al., 1997; Vermeer et al., 2003). In addition,
subclinical infarcts have been shown to be an independent predictor of
subsequent symptomatic stroke, and may be a surrogate marker of vascular
cognitive impairment (Bernick et al., 2001; Kobayashi et al., 1997; Vermeer et al.,
2003). Data from NOMAS suggest that the elderly, men, hypertensives, and
possibly younger black persons and Hispanics born in the United States, have a
disproportionately higher burden of subclinical infarcts (Prabhakaran et al.,
2008).
Markers of subclinical cardiovascular disease (such as carotid artery intima and media thickness, peripheral arterial disease, angina pectoris, and ankle-arm index) are associated with disease, disability, cognitive impairment, and successful aging (Kuller et al., 2000; McDermott et al., 2001; Newman et al., 2001; Newman et al., 2003; O’leary et al., 1999). But, the role of subclinical vascular brain disease in successful cognitive aging has not been examined.

The tremendous variability in the presence and severity of white matter hyperintensities, cerebral and ventricular atrophy, and subclinical infarcts documented in the literature implies that these findings are not merely senescent changes accompanying normal aging. The key objectives of this study were to examine the associations of successful cognitive aging and (1) brain atrophy and ventricular enlargement, (2) white matter hyperintensity volume, and (3) subclinical infarction, adjusting for sociodemographic factors and vascular risk.

7.2 Results

7.2.1 Sample Characteristics

The demographic characteristics of the sample with respect to age, gender, and race/ethnicity, are detailed in section 4.2.1, and education and socioeconomic status in section 5.2.1. Mean GVRS score was 8.6 ± 0.9. The prevalence of subclinical infarction was 16%. Mean white matter hyperintensity volume was 0.7 ± 0.8. Mean ventricular and cerebral volumes as a proportion of
total cranial volume were 3.2 ± 1.5 and 72.5 ± 4.2, respectively. Sample characteristics are shown in Table 7.2.1.

### 7.2.2 Odds of Successful Cognitive Aging by Subclinical Vascular Brain Damage Marker

Results of logistic regression analyses comparing the odds of successful cognitive aging for WMHV, ventricular volume, cerebral volume, and subclinical infarction, are shown in Table 7.2.2. Model 1 was unadjusted for sociodemographic and vascular risk, considering only age and the length of time between baseline and MRI. Model 2 added years of education and socioeconomic status. Model 3 included the NOMAS GVRS to account for vascular risk, as well as depressive symptoms, in addition to years of education and socioeconomic status, which are not already included in the GVRS, and length of time between baseline and MRI.

For every unit increase in log-WMHV, the odds of successful cognitive aging, adjusted for age, education, socioeconomic status, and length of time between baseline and MRI, were 18% lower (Model 2: OR=0.82, 95% C.I. 0.71-0.96; p=0.011); after further adjusting for vascular risk, the odds were attenuated but remained significant (Model 3: OR=0.84, 95% C.I. 0.71-0.99; p=0.035).

For every unit increase in log-ventricular volume, the odds of being in the successful cognitive aging group, adjusted for age, education, socioeconomic status, and length of time between baseline and MRI, were 29% lower (Model 2: OR=0.71, 95% C.I. 0.51-0.99; p=0.043); after further adjusting for vascular risk, the relationship was no longer significant.
Similarly, for every unit increase in cerebral volume, the odds of successful cognitive aging, adjusted for age, education, socioeconomic status, and length of time between baseline and MRI, were 5% greater (Model 2: OR=1.05, 95% C.I. 1.00-1.09; p=0.030), but after further adjusting for vascular risk, the relationship was no longer significant.

With respect to covariates, only GVRS and length of time between baseline and MRI were significant contributors to the adjusted models for WMHV, ventricular volume, and cerebral volume, suggesting that GVRS mediated the relationships between these variables and successful cognitive aging.

No statistically significant associations were found between subclinical infarction and successful cognitive aging.

7.3 Discussion

In this study, we examined the relationship between MRI markers of subclinical vascular brain disease and successful cognitive aging in a multi-ethnic cohort. In line with our hypothesis, we found that greater white matter hyperintensity volume was associated with lower odds of successful cognitive aging even after adjustment for global vascular risk. The significance of white matter hyperintensities is even less well understood than the potential causal factors associated with their development. Recent results from the Leukoaraiosis in Disability Study (LADIS) indicated that functionally independent elderly subjects with diffuse confluent WMH are at considerable rapid risk of becoming dependent due to motor and cognitive deterioration (Inzitari et al., 2007). Older
99 adults who were either not impaired or restricted in only one instrumental activity of daily living were classified as having mild, moderate, or severe WMH according to the Fazekas visual rating scale; just one year later, 9% of the mild, 16% of the moderate, and 24% of the severe groups were restricted on at least two instrumental activities. WMH are also associated with motor and gait impairments among the elderly, and may be correlated with poorer medication adherence (Bhadelia R et al., 2009; Insel et al., 2008). Taken together, these findings indicate that WMH may be an indicator of intensifying disability in older adults. Likewise, the implications of WMH for those managing with chronic illness(es) are also of relevance. Hypertension is consistently associated with WMH in the literature, for instance, but when high blood pressure is poorly controlled, the association is stronger and the burden of WMH greater (de Leeuw et al., 2002; Dufouil et al., 2001; Soderlund et al., 2003).

The presence and severity of white matter hyperintensities is repeatedly associated with global and selective cognitive functioning in cross-sectional studies (de Groot et al., 2000; Matsubayashi et al., 1992; Ylikoski et al., 1993). Greater WMH load is related to poorer performance, especially on tasks of processing speed and executive functioning (Cook et al., 2004; Gunning-Dixon and Raz, 2000; Fazekas et al., 2005; Wright et al., 2008). The progression of periventricular WMH is an important factor in cognitive decline, and is associated with reduced cognitive speed (Cook et al., 2004; van den Heuvel, 2006). With reduced cognitive speed purported to be the first manifestation of cognitive decline in old age, the early identification of periventricular WMH may abate
further decrements in cognition (Tisserand and Jolles, 2003). Moreover, recent studies using Diffusion Tensor Imaging (DTI) have shown diffuse microstructural damage even in white matter that appears normal on T1- and T2-weighted images (Shimony et al., 2009). This implies that WMH may represent significantly compromised white matter integrity, the functional consequence of which is impaired cognitive functioning, and perhaps, therefore, a lower likelihood of successful cognitive aging (Madden, Bennett & Song, 2009).

Although age appears to be the most robust predictor of WMH burden, the role of WMH in healthy aging is unclear (Raz & Rodrigue, 2006). Recent studies suggest that WMH likely reflect an increased vascular risk and the presence of vascular disease, even in a relatively healthy population, as vascular health has been found to be an important determinant of the proliferation of white matter lesions in community-dwelling older adults (Raz et al., 2007). Vascular disease is both treatable and preventable by existing medical and behavioral therapies, and treatment of risk factors such as hypertension has been found to reduce the impact of subclinical vascular brain disease, though not entirely eradicate neuropathology (Elmer et al., 2006; Korf et al., 2004; Moser, 2006; Raz et al., 2003). While our results imply that microvascular damage does not completely explain the relationship between WMH and successful cognitive aging, targeted risk factor interventions could prevent the onset of some WMH or delay their progression, and may improve the odds of successful cognitive aging.

In contrast to the association found for WMH and our original hypothesis, cerebral and ventricular atrophy do not appear to be significantly related to
successful cognitive aging in our population after adjustment for global vascular risk. Despite the assumed common vascular etiologies of WMH and brain atrophy, previous studies have shown that they are largely independent, suggesting that an alternate mechanism may account for the association between WMH and successful cognitive aging (Wiseman et al., 2004). This is evidenced by our findings that the NOMAS GVRS only somewhat attenuated the association between WMH and successful cognitive aging, but appears to mediate the associations between cerebral and ventricular atrophy and successful cognitive aging.

Contrary to our hypothesis, we did not find an association between the presence or absence of subclinical infarction and successful cognitive aging. Future research should address the location and number of infarcts, as the pattern of infarction may be more indicative of adverse outcomes than mere presence or absence (Baune, 2009).

7.4 Limitations

There are several limitations to our study. We do not have data on WMHV segmented by brain region, or on WMH progression, both of which have been associated with cognitive health (Silbert et al., 2009). Also, the methods used for the determination of WMHV are currently only applicable for research studies, though they are in keeping with recent harmonization standards for research on vascular cognitive impairment promulgated by the NINDS and Canadian Health Network (Hachinski et al., 2006). Additionally, there is a possibility of selection
bias in our sample, as the MRI sub-study group is somewhat healthier than the overall cohort due to a survivor effect, and has slightly lower prevalences of some comorbid risk factors.

Incidental findings on brain MRI, including the subclinical vascular pathologic changes examined here, are common in the general population, and, as they are associated with functional and cognitive dysfunction, cannot be ascribed to normal aging (Vernooij et al., 2007). In order to inform clinical management and facilitate successful aging, longitudinal studies and more sensitive techniques are needed to more comprehensively evaluate the natural course, prognosis, and etiologic risk factors of these structural brain changes, as are randomized trials of preventive therapies (Longstreth, 2005).
<table>
<thead>
<tr>
<th>Sociodemographic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMHV*</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>Quartile 1 (&lt;0.21)</td>
<td>300 (25.8)</td>
</tr>
<tr>
<td>Quartile 2 (0.21-0.36)</td>
<td>297 (25.6)</td>
</tr>
<tr>
<td>Quartile 3 (0.36-0.77)</td>
<td>282 (24.3)</td>
</tr>
<tr>
<td>Quartile 4 (0.77+)</td>
<td>283 (24.3)</td>
</tr>
<tr>
<td>Ventricular volume/cranial volume*</td>
<td>3.2 ± 1.5</td>
</tr>
<tr>
<td>Cerebral volume/cranial volume*</td>
<td>72.5 ± 4.2</td>
</tr>
<tr>
<td>Subclinical infarction</td>
<td>167 (15.5)</td>
</tr>
</tbody>
</table>

*Data given as mean (SD).

WMHV=White matter hyperintensity volume; GVRS=Global Vascular Risk Score
### Table 7.2.2. Odds of Successful Cognitive Aging by Subclinical Vascular Brain Damage Marker

<table>
<thead>
<tr>
<th>WMHV</th>
<th>Subclinical Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>Model 1†</td>
<td>0.82 (0.70-0.95)</td>
</tr>
<tr>
<td>Model 2*</td>
<td>0.82 (0.71-0.96)</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>0.84 (0.71-0.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ventricular volume/ Cranial volume</th>
<th>Cerebral volume/ Cranial volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>Model 1†</td>
<td>0.71 (0.52-0.97)</td>
</tr>
<tr>
<td>Model 2*</td>
<td>0.71 (0.51-0.99)</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>0.73 (0.52-1.03)</td>
</tr>
</tbody>
</table>

†Odds ratios are adjusted for age and length of time between baseline and MRI.
*Odds ratios are adjusted for age, years of education, socioeconomic status, and length of time between baseline and MRI.
‡Odds ratios are adjusted for NOMAS Global Vascular Risk Score, depressive symptoms, years of education, socioeconomic status, and length of time between baseline and MRI.
Chapter VIII. Conclusion

8.1 Summary and Recommendations

With both investigative and public health implications in mind, we endeavored to create an ecologically valid definition of successful aging that incorporates both physical well-being and cognitive abilities, advancing upon those used in previous studies. In building upon prior research on successful aging (e.g., Depp & Jeste, 2006; Newman et al., 2003), we strived to enable a deeper understanding of the predictors of successful cognitive aging, as well as identify of the vulnerable groups and modifiable risk factors to target for intervention.

We reported the overall prevalence of successful cognitive aging in a large cohort of multi-ethnic older adults, and described the extent to which the prevalence varies by age, gender, and race/ethnicity. In the NOMAS MRI cohort, the prevalence of successful cognitive aging was 37%, with 49% of adults meeting the disease and disability criteria and 87% meeting the cognitive criteria. The prevalence decreased with increasing age starting at age 60, with the sharpest decline in the oldest old aged 80 and above. While we found that women were less likely to be successfully cognitively aging than were men, we did not observe any differences in the prevalence of successful cognitive aging by racial or ethnic groups.

We examined several sociodemographic and psychosocial determinants of successful cognitive aging, and described the extent to which the prevalence of successful cognitive aging varies by education, literacy, and socioeconomic
status, and how it is associated with social resources and quality of life. While we did not find a significant difference in years of education among successful and non-successful cognitive agers, we did find a marginally significant association between literacy and successful cognitive aging among Spanish-speakers, which seems to imply that cultural factors may play a role in the relationship between literacy and successful cognitive aging. The prevalence of successful cognitive aging in NOMAS was significantly lower among those with a lower socioeconomic status. Individuals with fewer financial resources tend to experience poorer health, and have less access to health-promoting resources; interventions targeting successful cognitive aging should therefore include individual-level risk factor management, as well as public health strategies and social and political policies aimed at community improvement (Adler and Ostrove, 1999; Galobardes et al., 2006; Mirowsky and Ross, 2003).

The most frequently used measures of social status in epidemiological studies are education, income, and occupation – less is known about the influence of social resources on health outcomes (Liberatos et al., 1988). Several social network variables were important in successful cognitive aging: we found significant associations with marital status, number of times in the past week spent talking on the telephone, having someone to trust and confide in, and feeling lonely, but not number of friends, number of visits with friends/family, seeing friends/family as often as one would like, or having someone to help if one were sick or disabled. And, all domains of our quality of life index – activity, daily living, health, support, and outlook – as well as the quality of life index total score
were, significantly associated with successful cognitive aging. Multivariate logistic regression showed that in NOMAS, social resources and quality of life appeared to be more important predictors of successful cognitive aging than demographic variables alone, supporting the active engagement hypothesis of successful cognitive aging, which involves both being connected to other persons and engaging in productive activities (Rowe and Kahn, 1998). While our assessment of age, race and ethnicity, education and literacy, socioeconomic status, social resources and quality of life was certainly not all-inclusive, it does stress the need for the consideration of non-medical factors in assessments of successful cognitive aging, and encourages a paradigm shift in successful aging research from largely biomedical to more biopsychosocial.

Central to successful aging is a protective vascular risk factor profile, and studies strongly support an association between the presence of vascular risk factors and a lower likelihood of successful cognitive aging (Depp and Jeste, 2006; Gorelick, 2005). We not only found that the odds of successful cognitive aging decreased by almost one-third for every unit increase in NOMAS Global Vascular Risk Score, but we also observed a dose-response for increasing quartiles of GVRS. With early detection of at-risk persons crucial to the success of medical management and behavioral interventions, risk assessment tools such as the GVRS, which take into account multiple sociodemographic and cardiovascular risk factors simultaneously, may be a more effective means for guiding comprehensive prevention efforts and increasing the opportunity for successful cognitive aging.
Depressive symptomatology was also associated with a lower likelihood of successful cognitive aging in NORMAS. We found that those who did not meet criteria for clinical depression had a 64% greater odds of successful cognitive aging, and that the odds of successful cognitive aging were 2% lower for every one-point increase in CES-D score. Persons who were depressed at baseline had a 73% lower odds of successful cognitive aging compared to those who were not depressed at baseline or follow-up, while those who were depressed at both baseline and follow-up had a 78% lower odds of successful cognitive aging.

These findings have important implications for intervention, since the response to therapy and eventual outcome for depression are inversely related to their chronicity (Mynors-Wallis and Gath, 1997; Seivewright et al., 1998). And, with hypothalamic-pituitary-adrenal axis dysregulation related to many cardiovascular disease risk factors, treatment of depression may promote successful cognitive aging from a variety of angles (Agabiti-Rosei et al., 1983; Rosmond and Bjorntorp, 2000). Physical, cognitive, and emotional health are all key components of successful cognitive aging, so multidisciplinary approaches to the care of depressed older persons that integrate medical and psychiatric care are needed (Bartels et al., 2004; Unutzer et al., 2002).

Finally, we examined the relationship between MRI markers of subclinical vascular brain disease and successful cognitive aging in our multi-ethnic cohort. Cerebral and ventricular atrophy did not appear to be significantly related to successful cognitive aging in our population after adjustment for global vascular risk. In contrast, each unit increase in log-white matter hyperintensity volume was
associated with an 16% lower odds of successful cognitive aging even after adjustment for global vascular risk, suggesting that, despite the assumed common vascular etiologies of WMH and brain atrophy, an alternate mechanism may account for the association between WMH and successful cognitive aging (Wiseman et al., 2004). Subclinical vascular pathologic changes are common in the general population, and, as they are associated with functional and cognitive dysfunction, cannot be ascribed to normal aging (Vernooij et al., 2007). Targeted vascular risk factor therapies could prevent the onset of some of these brain changes or delay their progression, and may improve the odds of successful cognitive aging. However, to meet the challenge of identifying targets for intervention to promote successful cognitive aging begins with further research aimed at clarifying the etiology of subclinical vascular brain damage, particularly WMH.

8.2 Limitations

The use of a community-based multi-ethnic sample gave us the ability to study a representative range of physical and cognitive health components and sociodemographic and psychosocial characteristics of older adults, though there are several limitations to our study that are worth noting. The sample may have been biased due to a survivor effect, as the MRI sub-study cohort is somewhat healthier than the overall prospective cohort; and, our community-based sample did not include frailer populations living in institutions or care homes. Also, the manner in which successful cognitive aging is defined and measured
undoubtedly impacts prevalence estimates and observed associations. Social resources and quality of life were only assessed at one time point, so we did not know how they have changed over time, either up until and/or following their measurement. Our quality of life index and social resources questionnaire were fairly short and capture only some of the many psychological and physical manifestations of these broad concepts. Though subjective, these measures may better reflect the intensely personal and interpretable concept of successful cognitive aging as they represent individuals’ points of view.

The NOMAS GVRS has not been validated in other cohorts, though a major strength is that it is applicable to non-white subjects. Data on depression were captured using two different instruments: at baseline with the HDRS, and at the time of MRI with the CES-D. However, the efficacies (area under the receiver operating characteristic curve, AUC) of the CES-D and HDRS as screening instruments are comparable, and the CES-D has been found to be tightly correlated with various versions of the Hamilton form (Caracciolo and Giaquinto, 2002; Lewisohn, 1997). The CES-D does not provide criteria for the diagnosis of clinical depression; on the other hand, the scale does allow for the assessment of symptom severity, particularly within the eight to twenty percent of individuals who may have subsyndromal depression (Blazer, 2003).

Lastly, we did not have data on WMHV segmented by brain region, or on WMH progression, both of which have been associated with cognitive health (Silbert et al., 2009). Also, the methods used for the determination of WMHV are currently only applicable for research studies, though they are in keeping with
recent harmonization standards for research on vascular cognitive impairment promulgated by the NINDS and Canadian Health Network (Hachinski et al., 2006).

The field of successful aging requires more careful attention and study. In order to ultimately inform clinical management and facilitate successful cognitive aging, longitudinal studies and more sensitive and comprehensive measurement techniques are needed.

8.3 Future Directions

The biopsychosocial model was introduced by George Engel over thirty years ago:

To provide a basis for understanding the determinants of disease and arriving at rational treatments and patterns of health care, a medical model must take into account the patient, the social context in which he lives, and the complementary system devised by society to deal with the disruptive effects of the illness (Engel, 1977).

Yet, current models of disease remain predominantly biomedical, though Engel and others have recognized that it is the mutual influence of both basic physical phenomena and mental and social phenomena that contributes to the modulation of individual vulnerability to disease and disability (Borrell-Carrio et al., 2004; Engel, 1977; Fava and Sonino, 2008). This is particularly true with regard to successful cognitive aging, which likely encompasses at least four dimensions of health – physical, functional, psychological, and social (Phelan et al., 2004). The components of successful cognitive aging are interdependent and
synergistic, in that avoiding disease and disability makes it easier to maintain social integration, a good quality of life, and better cognitive health, and vice versa (Silverstein and Parker, 2002). Nevertheless, of the attempts to operationalize successful aging, few have been multidimensional, and none has emerged as standard (Depp and Jeste, 2006; Phelan and Larson, 2002).

To move forward, research into successful aging needs to extend beyond models of biological and cellular aging to include those psychological and sociologically-related factors associated with optimal functioning in older age (Lupien and Wan, 2004). Indeed, on the basis of the findings presented in this dissertation, consideration of such biopsychosocial factors as socioeconomic status, social support, quality of life, and depressive symptoms alongside novel indicators of disease and disability including global vascular risk and white matter hyperintensity burden, may lead to a more robust definition of successful cognitive aging replete with opportunities to modify the aging process. Some of the factors investigated in this study that have been found to distinguish the “happy-well” from the “sad-ill” are under at least some personal control (Vaillant and Mukamal, 2001).

Further research is needed, as the inclusion of additional criteria that have been associated with physical, cognitive, and/or psychosocial functioning, such as chronic kidney disease, and the relaxation of requirements to allow older adults with some loss of functioning to be categorized as successful agers, will help to further refine the concept of successful cognitive aging (McLaughlin et al., 2010). Only with an integrative perspective of successful cognitive aging will we
be able to meet the anticipated increases in aging populations and lengthening of life expectancies with postponement of functional impairments and maintenance of quality of life.

Theories in the field of aging remain largely deficit-driven, despite evidence that the brain exhibits functional plasticity in aging, and that older adults can experience positive changes in functional abilities and learn to use new strategies and technologies to adapt to age-associated declines (Czaja and Sharit, 2009; Greenwood, 2007). A better understanding of the determinants of successful cognitive aging, and the benefits associated with a valid and reliable model, is crucial to the development of therapeutic interventions and public health programs that will allow individuals to lead healthy, independent, and productive lives well into old age.
Bibliography

1. Abutaleb N. Why we should sub-divide CKD stage 3 into early (3a) and late (3b) components. Nephrol Dial Transplant. 2007;22(9):2728-2729.


44. Centers for Disease Control and Prevention (CDC) and the Alzheimer’s Association. The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health: Chicago, IL; Alzheimer’s Association, 2007.


173. Loring J, Dong C, Mora-McLaughlin C, Rundek T, Elkind MSV, Sacco RL, DeCarli C, Wright CB. Education moderates the association of


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