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Vascular Depression: An Early Indicator Of Decline

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VASCULAR DEPRESSION: AN EARLY INDICATOR OF DECLINE

by

DANIEL LEE PAULSON

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2013

MAJOR: PSYCHOLOGY (Clinical)

Approved by:

Advisor

Date

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ACKNOWLEDGEMENTS

I would like to thank my dissertation committee members – Drs. Peter Lichtenberg, John Woodard, Joseph Fitzgerald and Cynthia Arfken – for their helpful guidance, support and feedback throughout this process. In particular, I thank Dr. Lichtenberg for his supervision of my research, his development of independent coursework, his tireless efforts to develop and maintain the pre-doctoral training program at the Institute of Gerontology, and his willingness to partner me with more senior researchers, Dr. Bowen and Dr. Raykov in particular. I would also like to thank Dr. Lichtenberg for his patience as I have grown, both intellectually and interpersonally, into my role as a junior researcher. I would also like to thank Dr. Woodard for his dedication to my training as both a clinician and a researcher. I also wish to express my gratitude to the Institute of Gerontology at Wayne State University for offering excellent training opportunities in a collegial environment.

I thank Dr. Mary Elizabeth Bowen for her discussion of concepts in this dissertation and for her time and effort in training me on use of the Health and Retirement Survey dataset. Indeed, these are skills that I hope to use throughout my career, and this dissertation has been greatly facilitated by her expertise. I would also like to thank Dr. Tenko Raykov for his development of empirical methods presented in this dissertation and for his instruction on use of these methods.

I would also like to thank my wife, Kirsten, and daughters, Nadia and Gabriella, for their support throughout my time as a graduate student and doctoral candidate. I also thank my father, Dr. Peter Paulson, mother, Jane Paulson, and sister, Dr. Joanna Ganning for their thoughtful proofreading and support.

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CHAPTER 1

Introduction

“How can we transform to a normal and physiological condition, old age, at present utterly pathological, unless we first understand the most intimate details of its mechanism?”

-Eli Metchnikoff, 1908

Depression has been identified as a leading threat to overall health and a leading cause of disability, and in late life is associated with higher rates of morbidity and mortality (Blazer, 2003). A subtype of depression believed to be caused by high cerebrovascular burden, termed vascular depression, is particularly associated with cognitive decline (Mast, Yochim, MacNeil, & Lichtenberg, 2004) and disease of the central nervous system (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). Meanwhile, an emerging literature describes frailty as a self-perpetuating cycle of “multisystemic dysregulation of homeostatic systems,” with numerous risk factors and one likely outcome: death (Fried et al., 2001). Some researchers have noted epidemiological and phenomenological similarities between vascular depression and frailty and cognitive decline (Katz, 2004), but no cohesive model of relationships between these geriatric syndromes has been identified.

The objectives of this dissertation are to extend our knowledge of vascular depression by evaluating a series of hypotheses based on the concept depicted in Figure 1.1, of cerebrovascular burden, depression, frailty, cognitive decline and mortality. The model that will be evaluated conceptualizes these geriatric syndromes as reflecting consecutive phases of a single disease process involving global neurological decline. In this model, vascular depression symptoms are hypothesized to be a sensitive, early indicator of this disease progression.

Depression

Major depression occurs in 25% of women and 12% of men across the lifespan and has been identified as a major source of disability worldwide (Gelenberg, 2010). The base rate of the disorder varies across the lifespan, decreasing from a peak in early adulthood until the mid-70's, after which symptoms increase with age (Teachman, 2006). Though a diagnosis of major depression is based on whether a patient's number of symptoms meet a specific threshold (American Psychiatric Association, 2000), the number of depression symptoms experienced reflects a semi-continuous variable rather than a dichotomous one. Even modest elevations in depression symptoms are associated with higher levels of disability, loss of work, and reduced quality of life (Broadhead, Blazer, & George, 1990; Rapaport & Judd, 1998). Depression symptoms are of particular concern among elders, for whom subtle increases relate to impaired capacity for self-care (Stuck et al., 1999), deterioration of cognitive faculties (Crocco, Castro, & Loewenstein, 2010), and increased mortality risk (Arfken, Lichtenberg, & Tancer, 1999).

In clinical settings, depression is identified as the presence of at least one core symptom (depressed mood or lack of interest in activities) along with at least four of the following: feelings of worthlessness or inappropriate guilt, difficulty concentrating or decision making, fatigue, psychomotor agitation or retardation, hypersomnia or insomnia, significant weight loss or weight gain, and recurrent death or suicidal ideation (American Psychiatric Association, 2000). Based on the 8-item CESD used in the Health and Retirement Survey, endorsement of at least 3 symptoms corresponds to clinically-significant depression (Steffick, 2000). The behavior that is characteristic of depression can be conceptualized within a broader framework. Henriques proposed that the function of the central nervous system (CNS) is the regulation of behavior as described by an economic model (Henriques, 2003). He further proposed that depression represents the conservation of behavioral resources such as caloric energy and social capital

(Henriques, 2000). While depression represents an adaptive mechanism in Henriques's taxonomy, vascular depression differs in this respect. Vascular depression appears to result from the CNS degradation (Sneed et al., 2008), and so this depression subtype should be characterized as indicative of a broader disease process. Nonetheless, it still appears to result in conservation of behavioral resources marked by a decrease in social interaction and decline in self-care activities. Because these behavioral outcomes typically do not serve the elder well, vascular depression must be viewed as uniformly maladaptive.

Depression is broadly associated with adverse health outcomes. Individuals with depression have increased risk for stroke (Bos et al., 2008; Larson, Owens, Ford, & W., 2001; Salaycik et al., 2007), first heart attack (Glassman & Shapiro, 1998), and cancer (Penninx, Guralnik, et al., 1998). Additionally, depression has been associated with impaired immune functioning (Kiecolt-Glaser & Glaser, 2002; Salzet, Vieau, & Day, 2000) and the increase of proinflammatory cytokines, IL-6 in particular (Dentino et al., 1999; Lutgendorf et al., 1999; Maes et al., 1995; Maes et al., 1999; Maes, Song, Lin, De, & Van, 1998). Depression is associated with increased mortality (Arfken et al., 1999; Covinsky et al., 1999; Mehta et al., 2003), even after controlling for cardiovascular risk (Glassman & Shapiro, 1998). Furthermore, there is evidence for an interactive relationship between cognitive functioning and depression. For example, older adults with both depressive symptoms and cognitive deficits have a mortality risk three times that of their counterparts (Blazer, 2003; Mehta et al., 2003).

Vascular depression, a depression subtype characteristically observed among older adults, is the development of late-onset depression resulting from vascular burden related to such factors as diabetes and hypertension. Alexopoulos et al. (1997) hypothesized a relationship between late-onset depression (i.e., first episode of depression after age 65) and cerebrovascular

burden and later (1998) proposed that cerebrovascular distress predisposes, precipitates and perpetuates symptoms of depression in late life. The relationship between cerebrovascular burden and depression in late life can be described as a threshold effect whereby elders with two or more cerebrovascular risk factors (CVRFs) report more depression symptoms (Mast, Yochim, et al., 2004; Yochim, Mast, & Lichtenberg, 2003). Alexopoulos theorized that the behavioral and cognitive symptoms characteristic of vascular depression directly result from frontostriatal neuropathology of vascular origin. Behavior among individuals with late-onset depression is fundamentally vegetative, characterized by a marked loss of interest in activities (Alexopoulos et al., 1996; Lockwood, Alexopoulos, & vanGorp, 2002) and deep rumination (von Hippel, Vasey, Gonda, & Stern, 2008).

Cognitive Neurophysiology of Vascular Depression.

Decrement of inhibitory cognitive processes and corresponding neuropathology relate to vascular depression and underlie the fundamental connections between depression and other geriatric disorders emphasized in the present dissertation. Several avenues of research have recently examined the role of inhibition in cognitive functioning broadly speaking (Corbett, Constantine, Hendren, Rocke, & Ozonoff, 2009; Zanto & Gazzaley, 2009). Vascular depression is, in essence, the loss of cognitive inhibition relative to affective regulation. This specific form of cognitive decline signals the existence of diffuse neurological damage and precipitates additional neuropathology.

Numerous morphological differences, primarily relating to the frontal lobe and associated structures, have been identified as characteristic of depression. Often these differences are localized to the prefrontal lobe, but other findings suggest widespread morphological differences.

Postmortem studies indicate that individuals with depression have fewer glia in the dorsolateral prefrontal cortex (Rajkowska, Halaris, & Selemon, 2001; Rajkowska et al., 1999), amygdala (Bowley, Drevets, Ongur, & Price, 2002), the subgenual anterior cingulate and orbitofrontal cortex (Cotter, Mackay, Landau, Kerwin, & Everall, 2001; Ongur, Drevets, & Price, 1998). Abnormalities have also been reported in the entorhinal cortex as a result of depression (Bernstein, Baumann, Danos, Falkai, & Diekmann, 1998). Depression in late life has also been related to volumetric differences in the prefrontal cortex (Coffey et al., 1993; Goodwin et al., 1997), orbitofrontal cortical matter (Bremner et al., 2002), subgenual region of the anterior cingulate gyrus (Botteron, Raichle, Drevets, Heath, & Todd, 2002), hippocampus (Bremner et al., 2000), putamen (Husain et al., 1991) and caudate nucleus (Krishnan et al., 1992), in addition to others (discussed in Phillips, Drevets, Rauch, & Lane, 2003). Phillips et al. (2003) incorporate these findings with literature describing altered blood perfusion during depression to articulate a neurocircuitry-based model of depression involving relative impairment of executive functioning among otherwise healthy adults. Taken together, these findings suggest that late-life depression may be characterized by wide-spread neurological changes, likely related to wide-spread though subtle behavioral and cognitive changes.

In a similar vein, Drevets and colleagues (Drevets, Price, & Furey, 2008; Drevets et al., 1992) proposed a model describing how mood is modulated and expressed through a circuit extending from the left ventrolateral prefrontal cortex into the medial prefrontal cortical surface implicating the left amygdala. Greater activity along this pathway was found among individuals with depression, but not among depression-free individuals with a family history of mood disorders. This suggests that the activation observed in depressed participants may be a state-dependent process (Drevets et al., 1992). Drevets and colleagues (2008) elaborated on this

model by discussing the functional roles of other circuits in the management of affect. In addition to the circuit described in the 1992 paper, they described a visceromotor system that has connections with limbic structures, the hypothalamus and periaqueductal gray, which is responsive to affectively challenging stimuli. They further described a third pathway: an “orbital prefrontal network” that connects central and lateral orbital areas and includes sensory association areas, the inferior temporal cortex, the insula and the frontal operculum. They posit that this pathway is recruited for sensory integration and reward, aversion, and identifying relative value.

Von Hippel et al. (2008) argue that disconnection of a pathway conceptually similar to the one described by Drevets and colleagues (Drevets et al., 2008; Drevets et al., 1992) results in vascular depression. As these pathways traverse the subcortical prefrontal region, they may be vulnerable to cerebrovascular distress in this region. Consequently, von Hippel (2008) suggests that executive functions in general and the ability to attend to and inhibit depressogenic cognitions in particular become impaired. Such age-related inhibitory deficits have been reported in other areas of cognitive neuroscience research (Zanto & Gazzaley, 2009). They suggest impaired ability to inhibit depressogenic cognitions potentiates uncontrolled ruminative thinking, resulting in spiraling depression symptoms. Consistent with this hypotheses, von Hippel (2008) reported that ruminative thought mediates the relationship between executive functioning deficits and late-onset depression but not in depression among younger individuals. This pattern of relationships suggests that affective management deficits, resulting in depression, are a harbinger of a broader pattern of age-related cognitive and neurological decline.

Frailty

Frailty is conceptualized as the combined effects of life stress resulting in multi-systemic dysregulation of homeostatic systems. Although there are multiple models of frailty, Fried's (2001) conceptualization continues to be a leading model and the one utilized in the present dissertation. This model describes frail individuals as having at least three of the following conditions: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Fried (2001) reported that frailty is more common among individuals who are Black, have lower education and income, relatively poor health, and greater medical comorbidity and disability. In keeping with past research (Varadhan et al., 2009), the proposed dissertation will conceptualize frailty as the presence of at least three of five indicators of frailty including wasting (substantial weight loss), weakness, slowness, fatigue or exhaustion, and recent falls. Some studies suggest that frailty is more common among women (Fried et al., 2001), especially those with low education (Deeg, Portrait, & Lindeboom, 2002). Others suggest that men are at greater risk (Klein, Klein, Knudtson, & Lee, 2005), especially those who live alone (Deeg et al., 2002). Frail individuals experience decreased mobility, and heightened rates of activity of daily living (ADL) impairment, hospitalization and death (Fried et al., 2001; Lupon et al., 2008). The base rate of frailty is relative to age, with frequencies ranging from 3%-7% of individuals between ages 65 and 75 (Fried, 2003) and over 30% for individuals in their 90s (Walston et al., 2002).

Frailty is associated with comparably poor subjective health evaluations and higher age-adjusted rates of myocardial infarction, angina, congestive heart failure, peripheral vascular disease, arthritis, diabetes, hypertension and chronic obstructive pulmonary disease (Fried et al., 2001). It is noteworthy that frequencies of these comorbidities increase incrementally between robust (0 frailty symptoms), intermediate-frail (1 or 2 symptoms), and frail elders (3 or more

symptoms). One example of autonomic dysregulation associated with frailty is greater heart rate variability among frail elders (Varadhan et al., 2009). Moreover, the heart rate variability index used by these authors predicted mortality in the sample. Similarly, an index relevant to diabetes, insulin resistance as measured by homeostasis model assessment (IR-HOMA) scale was found to indicate more disordered metabolic functioning among frail elders (Barzilay et al., 2007).

Consistent with greater medical comorbidities associated with this syndrome, frailty also relates to higher rates of health care utilization. After adjusting for demographic variables, diabetes, stroke, hypertension, and hyperlipidemia, elders with 1-2 symptoms had odds ratios for overnight and emergency room hospital visits of 1.97 and 1.34, respectively. By contrast, frail elders (at least 3 symptoms) had odds ratios for overnight stays and emergency department visits of 4.45 and 3.10, respectively, by comparison to robust elders (Kiely, Cupples, & Lipsitz, 2009). Similarly, mortality risk escalates with increasing frailty. Individuals with just one or two symptoms of frailty have greater mortality risk than robust elders, and frail elders with three or more symptoms have even greater risk of death (Fried et al., 2001; Klein et al., 2005). Deeg et al.(2002) reported that frail women at age 66 have a 7.6 year life expectancy, which was considerably shorter than life expectancies for non-frail elders with other health profiles including those with cognitive disorders (23.4 years), cardiac disease (16.2 years), or cancer (20.2 years).

Depression and Frailty

Considerable research on frailty has included mental-health variables such as depression measures. However, much of this research does not explore depression as a direct cause of frailty and instead incorporates depression as a control variable or a suppressor variable. Andrew

and Rockwood (2007) reported that psychiatric disease broadly defined was relatively rare among the least frail elders, and was four times more common among elders who scored in the top decile of a frailty measure. However, interpretation of these results is limited by the use of cross-sectional, self-report mental health data, and the authors recognize the impossibility of developing a causal model of depression and frailty without longitudinal data. Nonetheless, considerable connections between depression and frailty indicators are implied by the literature.

For instance, findings suggest that fall risk, identified in the proposed dissertation as an indicator of frailty, is associated with depression (Allan, Ballard, Rowan, & Kenny, 2009; Anstey, Burns, von Sanden, & Luszcz, 2008; Byers et al., 2008; P. Thomas et al., 2009). Thomas et al.(2009) argue that age-related increases in fall risk are compounded by pathological brain changes, such as those observed in vascular depression. This argument was supported by reportedly greater fall risk among elders with both depression and executive dysfunction. Byers (2008) reported that elders who experienced adverse falls had 90% greater probability of experiencing significant depression. Though the relative contribution of depression and antidepressant medications to fall risk has been debated, (Kerse et al., 2008; Whooley et al., 1999), a thorough review of antidepressant use in late life suggests that the risk of fall associated with antidepressant use is similar to that in untreated depression (Darowski, Chambers, & Chambers, 2009).

In addition to the relationship between depression and falls, depression appears to predict other aspects of frailty. For instance, Thomas et al.(2009) presented results suggesting that depression and executive dysfunction, such as that observed in vascular depression, precipitate malnutrition, which can lead to wasting. In fact, depression has been identified as the leading cause of weight loss among nursing home residents (Morley & Kraenzle, 1994). Among older

men, depression was found to relate to steep decline in strength (Rantanen et al., 2000). Such muscle loss could contribute to slowness and weakness, both of which are characteristic of frailty. Depression was also found to be a strong predictor of ADL functioning and mobility problems over 6-years (Penninx, Leveille, Ferrucci, van Eijk, & Guralnik, 1999). Additional parallels between frailty and depression will be addressed below.

Cognitive Decline

Normative cognitive change in late life can be described as gradual changes affecting different facets of cognitive functioning such as processing speed (Salthouse, 1992a, 1992b, 1996), episodic memory (Naveh-Benjamin, Guez, & Shulman, 2004), or sensory function (Baltes & Lindenberger, 1997) that cause decline but do not severely handicap an individual's capacity for self-care. By contrast, catastrophic cognitive decline or terminal decline is identified as an accelerated loss of functioning preceding death. As an example, it was recently reported that elders with sharp declines on the Mini Mental State Exam experienced more ADL disability and higher mortality rates (Yaffe et al., 2010). While estimates of the temporal relationship between terminal decline and death vary, recent research identified evidence of terminal decline at a mean of 42 months before death (R. S. Wilson, Beck, Bienias, & Bennett, 2007). Another study reported that for individuals between 60 and 74 years of age, the relationship between cognitive functioning and mortality was negligible after controlling for health behaviors; however, impaired cognitive functioning significantly predicted incidence of death for individuals 75 years and older (Gillum & Obisesan, 2010). Between elders with similar levels of cognitive functioning, idiographic variability on measures of processing speed has been demonstrated to predict mortality (MacDonald, Hultsch, & Dixon, 2008). Though outside the scope of the

present dissertation, this finding suggests an interesting parallel between cognitive decline and frailty. Dysregulation in frailty is often characterized as greater variability.

While cognition can be assessed in very narrowly-defined terms, the present research conceptualizes cognitive functioning as a reflection of generalized neurological integrity that can be grossly assessed using a brief screening measure. For instance, performance on brief screens such as the Mini Mental State Exam is adversely affected by generalized cerebral atrophy, infarcts, periventricular white matter hyperintensities (WMHs; Prins et al., 2005) and ventricular volume (Jack et al., 2004). While brief screening instruments of gross cognitive functioning should not be used to diagnose geriatric cognitive disorders, performance on such instruments is predictive of dementia (Schultz-Larsen, Lomholt, & Kreiner, 2007) and mortality (Schultz-Larsen, Rahmanfard, Kreiner, Avlund, & Holst, 2008). Cognitive decrement among elders, regardless of etiology, produces deficits in ecological functioning.

Cognitive Decline in Relation to Depression and Frailty.

Several other studies are of particular importance in understanding late-life cognitive decline within the context of mood and longevity. Of particular relevance to the present dissertation, emerging research (Bielak, Gerstorf, Kiely, Luszcz, & Anstey, 2010) supports older findings (Butters et al., 2000) suggesting that depression symptoms precede terminal decline. With respect to longevity, research by both Mehta et al. (2003) and Arfken et al. (1999) suggests that the relationship between terminal cognitive decline and death is moderated by depression symptoms; elders with the most impaired cognitive functioning and the most depression symptoms were found to have the highest mortality risk. By contrast, other researchers have reported that among the oldest old, depression does not signal prospective loss of cognitive

functioning, but rather that cognitive decline at baseline indicates risk of increasing depression symptoms (Vinkers, Gussekloo, Stek, Westendorp, & van der Mast, 2004). Variability in these findings likely reflects a reciprocal, synergistic relationship between these factors.

While it is evident that a relationship exists between cognitive functioning and frailty, the direction of this relationship is not clear. For example, accelerated weight loss, such as that seen in frailty, precedes the onset of Alzheimer's disease (Johnson, Wilkins, & Morris, 2006). By contrast, a study of dementia-free elders, cognitive functioning at baseline and subsequent change in cognitive functioning predicted increasing frailty (Buchman, Boyle, Wilson, Yuxiao, & Bennett, 2007). Similarly, this variability likely signals close interrelationships between cognitive decline and frailty.

Vascular Depression as a Marker of Global Cerebral Disease Process

Vascular depression is conceptualized as a prodrome for frailty and cognitive decline. As described above, vascular depression has a neurological basis. As such, mood declines are hypothesized to result from the same neuropathology that causes frailty and terminal decline. Because mood is mediated by specific neurological pathways described above, it may be a more sensitive indicator of late-life neurological change than either cognitive or motor functioning. In this way, vascular depression may be a marker of global cerebral disease process and a harbinger of subsequent frailty, cognitive decline, and mortality.

Katz (2004) discussed considerable theoretical and phenomenological similarities and connections between depression and varying models of frailty. He notes that white matter disease, a common characteristic of abnormal cerebral aging, characterizes both late-onset mood disorders such as vascular depression and psychomotor deficits which can be symptomatic of

frailty. A corollary of this argument is that the cerebrovascular disease that causes prefrontal white matter hyperintensities and vascular depression could also lead to posterior white matter hyperintensities resulting in falls and other motor deficits such as slowness and weakness.

Atkinson et al. (2010) have made arguments that cognitive deficits and motor deficits appear to be related because they share a common cause: global central nervous system degradation. Atkinson and colleagues (2010) discuss how cognitive decline may precede deficits in motor functioning. Citing the finding that elders with progressive dementia demonstrate cognitive impairment often long before psychomotor functioning deficits (Njegovan, Man-Son-Hing, Mitchell, & Molnar, 2001), they hypothesized that cognitive functioning may simply be more sensitive to global neuropathology. This theory was further based on evidence that elders increasingly recruit frontal areas for basic cognitive functions as posterior structure atrophy accumulates (Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005). In this way, psychomotor deficits might be disguised while executive functioning declines. Maintenance of mood involves an elaborate network of fronto-striatal projections (Drevets et al., 2008), and appears to be very sensitive to neurological insult (Sneed et al., 2008). Consistent with Atkinson and colleagues' (2010) first argument, it may be that a decline in mood is an early indicator of global CNS neuropathology that is not yet severe enough to cause cognitive and psychomotor deficits such as those seen among frail individuals. In this way, vascular depression may be an early indicator of frailty and suggest a higher mortality risk.

Vascular dementia provides another example of how late-life depression can be a marker of global cerebral deterioration. Vascular dementia is identified clinically as diffuse cognitive impairment in the presence of multiple cerebrovascular risk factors and widespread WMHs on a T2 weighted MRI. These hyperintensities indicate areas of white matter disease, typically

caused by microstrokes, ischemic blockages of microvasculature, or other cerebrovascular disease. Among individuals with vascular dementia, subcortical WMHs were associated with decreased cerebral bloodflow and cortical atrophy (Schuff et al., 2009). Vascular depression and vascular dementia result from similar vascular factors. Vascular disease broadly speaking, and microbleeds in particular, have been identified as a leading predictor of mortality among a sample of patients with memory disorders, including vascular depression patients, regardless of memory disorder diagnosis (Henneman et al., 2009). Given the relationship between cerebrovascular burden and mood described above, these findings are consistent with the hypothesis that late-life depression may be a sensitive and clinically relevant indicator of an underlying disease process.

Another example of progressive decrement of mood, cognitive, and psychomotor functioning is Alzheimer's disease (AD). Alzheimer's accounts for the majority of late-life dementia diagnoses and poses a significant mortality risk to elders. Evidence of very modest cognitive decline distinguishes those at risk for diagnosis of Alzheimer's disease several years before significant memory impairments are noticed. This suggests gradual development of subclinical neuropathology over the course of many years. However, individuals typically do not manifest clinically-significant cognitive deficits until brain reserve, compromised by neuropathology, crosses an idiographic threshold (Satz, 1993). Consistent with the hypothesis that mood is a more sensitive indicator of global neurological decline, a growing body of research suggests that depression symptoms also precede Alzheimer's disease, often occurring within a year of clinically significant memory loss (Green et al., 2003). Moreover, neurofibrillary tangles and beta-amyloid plaques are more prevalent in Alzheimer's patients with significant

depression symptoms than those without (Rapp et al., 2008), further suggesting parallel underlying disease processes for Alzheimer's disease and at least some subtypes of depression.

Specific Hypotheses

This dissertation includes four separate empirical studies, each testing a hypothesis drawn from the theoretical model outlined above. The first paper tests the hypothesis that education, characterized as brain reserve, protects elders from development of depression symptoms secondary to high CVB-mediated neurological change. The second paper relates CVB, depression, and cognitive functioning to the three domains of Rowe and Kahn's (1997) successful aging theory, and use these variables to predict incidence of death. The third paper tests the hypotheses that vascular depression predicts incidence, and prevalence, of frailty. The fourth paper tests the theory that vascular depression predicts mortality indirectly through frailty.

CHAPTER 2

Does Brain Reserve Protect Older Women from Vascular Depression?

Abstract

Cerebrovascular burden (CVB) in contributes to neurological changes associated with new onset “vascular depression” in late life. Brain reserve theory, typically discussed in relation to dementia, was examined with regard to late life depression and cerebrovascular burden in older-old women. It was predicted that in a longitudinal sample (Health and Retirement Survey) of stroke-free women over the age of 80, higher levels of depression would be predicted by high CVB (more than two of the following: heart disease, diabetes, hypertension and lifetime history of smoking) and less educational attainment, after controlling for age and gross cognitive functioning. Depressive symptoms were assessed using the 8-item Center for Epidemiological Studies (CSED) measure, and cognitive functioning was measured using the 35-point Telephone Interview for Cognitive Status (TICS). Because of high attrition related to death and incapacity in this sample, multiple imputation based on self-rated health, activities of daily living and instrumental activities of daily living was used to specify missing data. A latent growth curve was used to identify differences in depression at baseline and over time based on CVB, cognitive functioning, education and age. Results indicate that at any level of CVB, older women with more education experienced fewer depression symptoms. Results support brain reserve theory and the vascular depression hypothesis. These results suggest that having greater education may postpone development of clinically-significant depressive symptoms resulting from high CVB, thereby preserving mood in late life.

Introduction

Depression is both common and medically relevant in late life. One recent study of 335 community dwelling older adults reported a normative increase in depression symptoms after the age of 77 (Teachman, 2006). The negative impact of depression in late life is highlighted by previous findings that depression was identified as the leading cause of disability worldwide, and that depressive symptoms in late-life predicted cognitive decline, higher levels of disability, and mortality (Blazer, 2003). The importance of mood as a clinical indicator of depressive symptoms is underscored by its utility in predicting these adverse health outcomes. Specifically, self-reported depressive symptoms were found to predict increased stroke risk (Bos et al., 2008; Larson et al., 2001; Salaycik et al., 2007), first heart attack (Glassman & Shapiro, 1998), and cancer (Penninx, Guralnik, et al., 1998), impaired immune functioning in general (Kiecolt-Glaser & Glaser, 2002; Salzet et al., 2000) and the increase of proinflammatory cytokines, IL-6 in particular (Dentino et al., 1999; Lutgendorf et al., 1999; Maes et al., 1995; Maes et al., 1999; Maes et al., 1998), and increased mortality (Arfken et al., 1999; Covinsky et al., 1999; Mehta et al., 2003).

Late Life Depression subtype: Vascular Depression

One attempt to better understand late life depression has been the Vascular Depression hypothesis (Alexopoulos et al., 1997a). Vascular depression theory suggests that cerebrovascular burden (CVB) may predispose, precipitate and perpetuate symptoms of depression in late life (Alexopoulos et al., 1997b). Cerebrovascular burden predicts diffuse deterioration in the central nervous system (C. J. Wilson, Finch, & Cohen, 2002), and prefrontal white-matter hyperintensities in particular (Coffey, Figiel, Djang, & Weiner, 1990; Raz, Rodrigue, & Acker, 2003). Late-life depression was associated with damage to frontostriatal white matter tracks,

termed white matter hyperintensities (WMHs; Fujikawa, Yamawaki, & Touhouda, 1993; Krishnan, Hays, & Blazer, 1997). WMHs in late life were associated with cerebrovascular burden (Cohen et al., 2009) and executive functioning deficits (Raz et al., 2003). When found in greater magnitude, WMHs predated late-onset depression (Nebes et al., 2002), but not depression among middle-aged individuals (Salloway et al., 1996). Our research group found that clinically-defined vascular depression was best measured as a threshold effect whereby elders with two or more cerebrovascular risk factors (CVB group) have more depressive symptoms than those with 0 or 1 risk factor (Mast, Azar, & Murrell, 2005; Mast et al., 2008; Mast, Yochim, et al., 2004; A. J. Thomas et al., 2001; Yochim et al., 2003). Importantly, older adults with both depression symptoms and cognitive deficits have a three times higher mortality risk than their counterparts (Blazer, 2003; Mehta et al., 2003), making cognitive functioning an important control variable in studies of this kind.

Most studies of vascular depression have mixed middle aged, younger old (65-79 years) and older old (80+) together (Alexopoulos et al., 1997a; Luijendijk, Stricker, Hofman, Witteman, & Tiemeier, 2008; Mast, Yochim, et al., 2004; Mehta et al., 2003). This methodology may mask some of the unique vascular depression patterns in the oldest old. Women over 80, in particular, represent the fastest growing target group for medical and behavioral interventions to enhance longevity and reduce morbidity. Between 2004 and 2006, the percentage of women in the U.S. over age 85 grew by 40% (U.S. Bureau of the Census, 2004, 2006). Moreover, by comparison to men, older women also have higher rates of depression, longer life expectancies, and experience more years of disability (von Strauss, Agüero-Torres, Kareholt, Winblad, & Fratiglioni, 2003). Thus, research examining the relationship between cerebrovascular burden and depression

among older women may inform interventions designed to effectively reduce dependence, the need for health and social services, and medical care costs in later life (see Blazer, 2003).

Vascular depression, like dementia, is associated with progressive neuropathology that results in behavior changes. Among neuropathological markers associated with late life depression, prefrontal WMHs, characteristic of high cerebrovascular burden (CVB; Cohen et al., 2009) are the most robust indicator. For instance, both prefrontal white matter hyperintensities (WMHs; Coffey et al., 1990; Nebes et al., 2002) and hippocampal volume loss (Ballmier et al., 2008) are associated with depression in late-life, but not in mid-life (Salloway et al., 1996). Late-life depression has also been related to differences in volumetric measurements of the caudate nucleus (Krishnan et al., 1992) and the dorsolateral prefrontal cortex (A. J. Thomas et al., 2003), in addition to differences described elsewhere (Wright & Persad, 2007).

Vascular Depression and Brain Reserve

Brain reserve theory has been proposed as an explanation for why considerable inter-individual variation exists with regard to behavioral response to brain changes. Experiences in early life, such as education, for example, are associated with greater synaptic density, described as brain reserve capacity (Stern, 2002). Years of education appears to be the most commonly-used indicator of brain reserve (Valenzuela & Sachdev, 2006b). As demonstrated by the Nun study (Mortimer, Snowdon, & Markesbery, 2003) individual response to neurological change is moderated by individual factors such as educational attainment in early life. Sixteen of the 34 nondemented, but highly educated sisters had neuropathology consistent with Alzheimer's disease. Some synaptic loss is characteristic of late-life brain changes; however, passive brain reserve theory posits that significant behavioral pathology develops only when synaptic availability declines past an idiographic threshold (Stern, 2002). Using Alzheimer's disease as an

example, Stern (2002) describes how educational experiences impart greater synaptic complexity and thereby reduce expression of clinically-significant cognitive deficits. Similarly, two complementary meta-analyses of 22 brain-reserve related cohort studies representing over 29,000 participants found that education and preference for stimulating leisure activities protected against cognitive decline (Valenzuela & Sachdev, 2006a), and that education, intellectual functioning, occupational functioning, and preference for stimulating leisure activities, all were associated with reduced incidence of dementia by around 50% (Valenzuela & Sachdev, 2006b). In a sample of 872 older participants, more education reduced the risk of dementia at any level of neuropathology based on cortical atrophy, hippocampal atrophy, or Braak stage (EClipSE Collaborative Members, 2010). A complex array of mechanisms ranging from variability in brain-derived neurotrophic factor to compensatory network recruitment have been proposed to explain how brain reserve translates into preserved cognitive functioning (Valenzuela, Breakspear, & Sachdev, 2007).

Given the neurological basis of vascular depression, it may be valuable to investigate the brain reserve hypothesis in a geriatric sample. Brain reserve theory predicts that well-educated individuals may have fewer depression symptoms in late life, even in the face of cerebrovascular burden. Consistent with this hypothesis, a large, multinational cross-sectional study reported a relationship between educational attainment and depression in later life, independent of socioeconomic conditions (Ladin, 2008) such that participants with greater education had lower rates of depression. This study did not examine, however, the influence of either CVB or education on the development of depression symptoms over time and did not employ a measure of cognitive functioning. Similarly, Schoevers and colleagues (2003) found that in a sample aged

65-84 years, having 8 or fewer years of education related to greater chronic depression for men, but not for women. Less research has evaluated these relationships among the older-old.

Purpose of the Study

The aims of this longitudinal study are to examine how CVB and education predict number of depressive symptoms at baseline, and the development of depressive symptoms over time in a sample of women in the community over the age of 80. Specifically, we will investigate whether higher levels of education postpone the rise of depressive symptoms in the face of Cerebral Vascular Burden. Broadly speaking, brain reserve theory suggests that the normative late-life rise of depressive symptoms, a behavioral marker of cerebral decline, will be postponed among elders with more education. Does this pattern hold even when CVB is present? This study also aims to measure rates of vascular depression, more akin to clinical research, by using established cutoff scores and examining rates of depression by CVB and education.

Hypothesis 1: Older adults with CVBs will have greater symptoms of depression at baseline and across the six year follow up period. Additionally, the relationship between CVBs and depression symptoms will be moderated by education whereby education will protect against development of depressive symptoms.

Hypothesis 2: Older adults with lower levels of education will have greater symptoms of depression at baseline and across the six year follow up period.

Hypothesis 3: Regardless of CVB level, brain reserve theory predicts that older adults with more education will have delayed onset of late-life depression symptoms. As such, fewer depression symptoms at baseline may predict greater development of symptoms, indicated by greater slope in depression symptom development, over the course of the study.

Method

Sample

The Health and Retirement Survey (HRS) is a prospective cohort study conducted by the University of Michigan with support from the National Institute on Aging. The first wave of the HRS occurred in 1992 with a 51 to 61 year-old cohort and was merged with the older (70 years and older) Asset and Health Dynamics of the Oldest Old Study (AHEAD) cohort in 1998. Two additional cohorts were added in 1998 to fill in the gaps between these two groups. Briefly, the HRS is a multistage probability cohort sample of U.S. households. Further details on the HRS design and methods have been previously published (Heeringa & Conner, 1995).

Four waves of data (1998 to 2004) from the HRS and the RAND Center for the Study of Aging were analyzed in this study ("RAND HRS Data, Version F," 2006). We analyzed data from 1,355 community-dwelling older women who were 80 years or older in 1998. Respondents were excluded if they were unable to complete testing without assistance (proxy). Because stroke is associated with subsequent depression symptoms (Bour et al., 2009), respondents were excluded from this study if they reported a history of stroke. Over the course of this study (years 1998 – 2004), the combined year response rate was 37.9% and wave-to-wave re-interview response rates ranged from 73.0% (2000) to 74.4% (2002). The baseline characteristics of the sample are displayed in Table 1. Of the 1355 individuals with complete baseline data, 514 completed the CESD scale across all waves of this study. Attrition rates in the HRS are comparable to that of other panel surveys (Groves & Couper, 1998) and sample attrition has not significantly influenced the representativeness of the remaining sample based on demographic, economic, and health measures (Cao & Hill, 2005). However, women over age 80 have higher mortality rates than the general population. Respondents missing by the end of the study (year

2004) were older ($t=-11.654, p<.001$), with fewer years of education ($t=4.593, p<.001$), more likely to have high CVB ($X^2=15.987, p<.001$) and depression scores ($U=187997.5, p<.001$) and lower TICS scores ($X^2=117.6, p<.001$) than their counterparts. Of the 808 respondents lost between baseline and 2004, 605 were identified as deceased and the vast majority of the remaining 202 respondents responded by proxy, suggesting incapacity. The sample is described in Table 2.1.

Measures

Depression

The dependent variable, depression symptoms, was measured by a Center for Epidemiologic Studies—Depression scale (CES-D)(Radloff, 1977). Respondents were asked if they were depressed, if everything was an effort, if their sleep was restless, were happy, lonely, enjoyed life, felt sad and could not get going (yes/no within the week prior to the interview). Higher CESD scores reflected more depressive symptoms and a CESD score ≥ 3 was used to indicate clinical depression (Steffick, 2000). The 8-item CES-D has similar symptom dimensions as the 20-item CES-D and past research suggests high internal consistency ($\alpha = .77$) and validity of the CES-D as implemented in the HRS (Steffick, 2000; Wallace et al., 2000).

Cerebrovascular Burden

Cerebrovascular burden (CVB) was based on doctor diagnosed self-reports of hypertension, heart disease, diabetes and smoking. At baseline, respondents were asked if a doctor had ever told them that they had these conditions (i.e., measure of prevalent conditions). In later survey waves, respondents were asked if they had been told by a doctor (since the prior interview) that they had developed any of these conditions. Reasonable concordance values between self-reports of disease and medical chart reviews have been reported (Bush, Miller,

Golden, & Hale, 1989; Psaty et al., 1995). Consistent with previous work (Mast, MacNeil, & Lichtenberg, 2004; Mast, Yochim, et al., 2004; Yochim et al., 2003), respondents were categorized into low and high cerebrovascular burden (CVB) groups based on the report of either low (0-1) or high (2-4) CVB risk factors.

Demographic Variables

Age was calculated based on reported birth date. Education was assessed as self-reported years of formal schooling. Participants were identified as having low (12 years or less) or high (more than 12 years) of education.

Cognitive Functioning

Cognitive functioning was measured by the modified Telephone Interview for Cognitive Status (TICS) included in the AHEAD/HRS data (Ofstedal, Fisher, & Herzog, 2005). This test is based on the older TICS measure published by Brandt, Spencer and Folstein (1988) and is a brief standardized test developed for remote screening of cognitive disorders. Because cognitive functioning has been identified as a confounding variable in the relationship between CVB and depressive symptoms (Mast, Yochim, et al., 2004), it was controlled for using this brief cognitive screen. TICS measures orientation, concentration, short-term memory, mathematical skills, praxis and language with the maximum score of 35 reflecting higher cognitive functioning. The TICS has high test-retest reliability and is generally sensitive to cognitive impairment (Brandt et al., 1988; Desmond, Tatemichi, & Hanzawa, 1994; Järvenpää et al., 2002; Welsh, Breitner, & Magruder-Habib, 1993). The sample was divided into low (scores lower than 17) and high (score of 17 or greater) scoring groups using a median split of TICS scores.

Auxiliary Variables

Self-rated health was assessed using the question, “Would you say your health is excellent, very good, good, fair, or poor?” The self-rated health Self-rated health has been identified as a leading indicator of mortality across studies, including the HRS/AHEAD sample (Siegel, Bradley, & Kasl, 2003). The Activities of Daily Living (ADLs) scale assessed self-reported difficulty walking across a room, getting in and out of bed, dressing, bathing and eating and produces a score ranging from 0-5. Instrumental Activities of Daily Living (IADLs) was measured using a 3-question instrument including items assessing difficulty with using the telephone, taking medication and handling money and produces a score ranging from 0-3. Cumulatively, these variables accurately identified 79.4% of the attrited participants, and all three variables significantly predicted attrition ($p \leq .001$).

Statistical Methodology

Longitudinal research with the older-old is complicated by attrition reflecting the extremely high mortality risk and threat of incapacity. It has been argued that in cognitive aging research, disregarding participants with missing data resulting from death or drop-out results produces a systematic underestimation of disorder severity and only the most robust elders are represented (Rabbitt, Lunn, & Wong, 2008). McArdle and Hamagami's (1991) seminal work used maximum likelihood estimation to analyze longitudinal datasets with significant missing data. More recently Graham (2003) has built on this methodology by including auxiliary variables in the imputation of missing data. Like cognitive decline, depression predicts mortality and incapacity in late-life. For this reason, it is appropriate to utilize an analytic strategy that permits inclusion of baseline respondents who attrite over the course of the study.

Data were analyzed using a latent growth curve (LGC) modeling approach specifically designed to account for missing data (e.g., Enders, 2010). This aim was achieved within the full maximum likelihood (FIML; e.g., Arbuckle, 1996) estimation framework with informative covariates. To this end, use of suitably chosen auxiliary variables was made (e.g., Graham, 2003), which represents a modern principled method for dealing with missing data that is implemented in the popular latent variable modeling software *Mplus* (Muthen & Muthen, 2010). Specifically, variables that were judged on substantive grounds to be related to the missing values were utilized as auxiliaries in all models fitted to address the research questions pursued in this paper. These variables were self-rated health, activities of daily living, and instrumental activities of daily living. In this way, data from all 1355 subjects in the available sample was used, regardless of number of repeated measures of depression that each one of them provided. In addition, through the inclusion of the above auxiliary variables, important information about the missing values – as contained in those variables – was incorporated into the model fitting and parameter estimation process (e.g., Little & Rubin, 2002). For all LGC models reported in this article, we used the robust maximum likelihood method of estimation (e.g, Muthen & Muthen, 2010) to handle some marked deviations from normality in their dependent variables.

In order to develop the (unconditional) LGC model, we examined the patterns of temporal change in depression using the Intercept-and-Slope model (IS model; e.g., Raudenbush & Bryk, 2002; Raykov & Marcoulides, 2008). This unconditional model does not include predictors and correlates of change patterns, while describing the individual development over time in depression as following a linear regression with assessment occasion playing the role of predictor variable. Specifically, this two-level model is based on the subject-level (level-1) equation

$$(1) \quad y_{it} = a_i + b_i (t-1) + e_{it},$$

where y_{it} is the depression score of the i th elderly person at t th assessment occasion ($t = 1, 2, 3, 4$), a_i and b_i are his/her starting position (initial depression) and rate (slope, gradient) of change in depression over time, and e_{it} is the associated error term (use of $t-1$ as a formal predictor allows interpretation of the intercept a_i as a starting position in depression, i.e., initial depression; e.g., Raudenbush & Bryk, 2002; $i = 1, \dots, n$, with $n = 1355$ denoting sample size).

The level-II model specified fixed and random effects for CVB (dichotomized), cognitive functioning (dichotomized), education (continuous), age (continuous), and the interaction of CVB and education. Then, a latent-growth curve was used to assess how these variables predicted change in depression over time. Finally, a post-hoc model was developed based on results of the previous latent-growth model, omitting the CVB by cognitive functioning interaction term.

In addition to the use of latent growth curve models, we completed a basic threshold analysis using CVB and education to predict frequency of probable depression in surviving participants at each wave. Consistent with the latent growth curve model, CVB was dichotomized so that respondents with 2 or more risk factors were identified as high CVB and those with 0 or 1 risk factor were identified as having low CVB. The education variable was also dichotomized so that those with 0-12 years of education were in the low education group and those with more than 12 years were in the high education group. Respondents with probable depression were identified as having a CES-D cutoff score of 3 or more and 5 or more based on recommended liberal and conservative clinical cutoffs for this instrument (Steffick, 2000).

Results

Level-I Model

The IS model defined in Equation (1) was then fitted to the data from the four repeated assessments of depression, and found to be associated with the following fit indexes (e.g., Raykov & Marcoulides, 2006): chi-square (χ^2) = 4.078, degrees of freedom (df) = 5, associated p -value (p) = .538, and root mean square error of approximation (RMSEA) = 0, with a 90%-confidence interval (0, .034). Goodness of fit indexes indicated a tenable model, and the linear change model adequately described the four waves of depression data. Nonlinear models were also explored but the linear equation (as opposed to quadratic) was a better fit to the data.

Next, we examined the estimates of the means and variances of the random effects (intercept and slope, i.e., starting depression and rate of its change) in this model. The estimate of mean starting depression (mean intercept) was 2.112, with a standard error (SE) of .052, and associated p -value $p < .001$, indicating significant mean initial depression level as could be expected. The mean slope was estimated at .034, SE = .026, $p = .191$. This result indicated that the average slope (rate of change over time in depression) was not significant in the sampled population.

Level-II Model

To gain further insight into these findings, we examined the individual differences in starting position and rate of change in depression, as reflected in the variances of these two random effects (intercept and slope). Specifically, the variance of initial depression was estimated at 2.353, SE = .194, $p < .001$ (two-tailed), indicating that there were significant individual differences in starting depression. The variance in the rate of temporal change in depression was estimated at .142, SE = .046, $p = .002$ (two-tailed), i.e., also significant. This finding indicated that while the average slope of depression change over time was not significant, there were considerable individual differences in the rate of change in depression –

some elderly increased while others decreased in their depression. Thereby, the correlation between starting position and rate of change in depression was estimated at .262, SE = .102, p = .010. This result indicated (unconditionally) that lower starting levels of depression were associated with higher rates of changes in depression over time.

Conditional Latent Growth

While the unconditional IS model examined the patterns of change in depression over time, it did not explain individual differences in these patterns in terms of other variables. To address this question, we fitted next the conditional IS model that explained individual differences in starting depression and rate of change in it in terms of individual differences of CVB (dichotomous; denoted next x_1), cognitive functioning (dichotomous; x_2), education (continuous; x_3), age (continuous; x_4), and the interaction of CVB with education (x_5). Specifically, this conditional model was defined by the following equations (e.g., Raudenbush & Bryk, 2002; Raykov & Marcoulides, 2008):

$$(2) \quad y_{it} = a_i + b_i(t-1) + e_{it},$$

$$a_i = \pi_{00} + \pi_{01}x_{1i} + \pi_{02}x_{2i} + \pi_{03}x_{3i} + \pi_{04}x_{4i} + \pi_{05}x_{5i} + \delta_i,$$

$$b_i = \pi_{10} + \pi_{11}x_{1i} + \pi_{12}x_{2i} + \pi_{13}x_{3i} + \pi_{14}x_{4i} + \pi_{15}x_{5i} + \omega_i$$

($i = 1, \dots, n$). When fitted to the data, this two-level model was found to be associated with the following fit indexes: $\chi^2 = 6.706$, df = 15, p = .965, RMSEA = 0, with a 90%-confidence interval (0, .001). These goodness of fit measures indicate a tenable model. Its parameter estimates of particular interest for this paper are presented in Table 2.2.

Post-Hoc Conditional Latent Growth Model

As seen from Table 2.2, the CVB and education interaction was found to be non-significant, controlling for age and cognitive functioning as well as the main effects for CVB and education. In the next fitted model, we dispensed with this interaction, i.e., fitted the LGC model defined in Equations (2) without the predictor denoted x_5 (interaction term). This more parsimonious model was similarly associated with tenable fit indexes: $\chi^2 = 5.896$, $df = 13$, $p = .950$, $RMSEA = 0$, with a 90%-confidence interval (0, .001). Its parameter estimates of particular relevance for this paper are presented in Table 2.3, and mean scores generated based on these results are displayed in Figure 2.1.

The top panel results in Table 2.3 suggest that once controlling for age, CVB and cognitive functioning, education explains a significant portion of individual differences in initial depression. Thereby, for respondents of the same age, CVB and cognitive functioning level, those with higher education had lower starting levels of depression. Similarly, CVB is uniquely significant after controlling for age, education, and cognitive functioning. That is, older adults with higher cerebrovascular burden show higher level of depression at start of study. Both age and cognitive functioning, however, are not uniquely significant. For otherwise-similar respondents, neither age nor cognitive functioning are associated with higher/lower initial depression.

The lower panel of Table 2.3 indicates that only education has unique predictive power with respect to rate of change in depression. Specifically, for elderly of the same age, with CVB and cognitive functioning, higher education is associated with higher rates of change in depression. We stress however that respondents with higher education tend to be among those with lower starting position on depression, as indicated in the top panel of Table 2 and mentioned above. We also note that this finding is consistent with the earlier indicated result of

significant and negative correlation between starting position and rate of temporal change in depression, which was obtained with the unconditional IS model fitted and reported first in this section.

Last but not least, the lower panel of Table 2.3 also indicates that none of the remaining three predictors is associated with unique explanatory power with regard to individual differences in rate of change in depression. That is, age, CVB, and cognitive functioning do not explain differences in rate of change in depression once accounting for the remaining three predictors of this quadruple of explanatory variables.

Threshold Analysis

Relative frequencies of clinically significant depression between respondents with high and low CVBs and education were compared using chi-square tests of independence. Respondents were initially identified as having probable depression if they had CESD scores equal to or greater than 3. To ensure that this result was not exclusively attributable to high base rates of probable depression in a large sample, these analyses were repeated with the probable depression group identified as those with CESD scores of 5 or more.

Using a cut-score of 3 on the CESD, a base rate for likely depression was identified as 33.5%. Using a cut-off score of 5 on the CESD produced a 14.8% base rate of probable depression. Illustrated in Table 4, all comparisons in both analyses using the more or less stringent cut score, indicated greater frequencies of probable depression among respondents with high CVBs and 12 years or less of formal education. Post-hoc analyses using stepwise logistic regression to predict membership in the “likely depression” group based on education, CVB and

an education*CVB interaction term produced results similar to those in Table 2.4. Inclusion of the interaction term did not improve prediction of probable depression (results not shown).

Discussion

The primary purpose of this paper was to determine whether education reduces the rate of depression in late life, and if so, whether this pattern reflects postponement of the onset of depression symptoms in older-old women. The present results indicate that more education predicts fewer depressive symptoms among women over the age of 80. Interestingly, older women with more education reported fewer symptoms at baseline, but more rapid development of symptoms over the course of the study. Moreover, the relative benefits of education was robust regardless of CVB level. Depression symptoms at baseline were also significantly predicted by CVB. In this sample, it was also found that probable depression was less likely among older women with post-secondary education. Consistent with past research, high CVB predicted greater risk of probable depression (Mast, Neufeld, MacNeill, & Lichtenberg, 2004; Mast, Yochim, et al., 2004; Yochim et al., 2003).

The finding that educational attainment relates to fewer depression symptoms in late life is consistent with previous work based on cross-sectional samples (Ladin, 2008) and research with limited longitudinal data (Schoevers et al., 2003). By contrast to existing literature, Schoevers et al (2003) reported that the relationship between education and depression was found for older men, but not older women. In the present sample, this relationship was robust among women over the age of 80. This difference may relate to Schoevers and colleagues' delineation of "low education" group as those with 8 years of education or less; a group that included 42.4% of their sample (Schoevers et al., 2000). By contrast, the multi-level model employed in the present study described the effect of education as a continuous variable. The

present research builds on these findings by examining longitudinal development of depressive symptoms in an older-old sample. Additionally, these findings suggest that Stern's (2002) conceptualization of brain reserve capacity, characterized by differential frequencies of symptom threshold by education, is applicable to the late-life development of depression symptoms. These results also support neurological functioning as a significant component of late-life depression (Sneed et al., 2008; von Hippel et al., 2008).

These findings are also generally consistent with the vascular depression hypothesis (Alexopoulos et al., 1997a) and previous findings (Mast, Yochim, et al., 2004; Mehta et al., 2003) relating CVB and late-life depression. The finding that threshold levels of CVBs predict both number of depression symptoms as well as probable depression has important implications for clinicians. Although research on the mechanisms of vascular depression will continue to evolve, primary care practitioners can use this simple method of calculating cerebrovascular burden as a guide to heightened risk of depression in older patients. The longitudinal data suggests limits for brain reserve. The current study found that those with higher burden reported increased depression over time, regardless of level of education. This is consistent with Sternberg's concept of passive brain reserve in that the reserve is protective until enough assault due to vascular factors overwhelms the protection of reserve. Brain reserve postpones, but does not preclude, the development of depression symptoms for elders with high CVB.

The finding that elders with fewer symptoms at baseline tended to have greater education, and experienced a greater increase in depressive symptoms throughout the course of the study suggests two possible interpretations. One explanation may be that less-educated respondents, with greater depression symptoms at baseline, were closer to a ceiling on the CESD instrument used in this study. This is unlikely, however, given that group means suggest mean levels of

depressive symptoms far from the measure's maximum score. A more likely, and theoretically-consistent explanation of this finding is that those with lower levels of depression at baseline, predominantly those with low CVB and comparably more education, are later in experiencing the normative late life increase in depression symptoms described by Teachman (2006). By contrast, the apparent plateau in depressive symptom development observed among those with greater symptoms at baseline, those with greater CVB and less education, may reflect a later point on this normative depression curve.

These results suggest several opportunities for further research. Specifically, it is known that educational quality relates to neuropsychological test performance (Manly, Jacobs, Touradji, & Small, 2002); however, there are no measures of educational quality in the HRS data. Quality of education may better predict depression (and in fact, cognitive functioning) in late life than years of education. Finally, as the HRS lacks information on the severity of CVB indicators, this study could not determine the effect of disease severity on the development of depression symptoms over time. Despite these limitations, the findings from this study suggest that CVB and education are associated with depression in late life. Future work may develop on these findings to examine how CVB interacts with other variables such as depression symptoms to predict the incidence of, or time to, death among the older-old.

CHAPTER 3

Successful Aging and Longevity in Older Old Women:

The role of Depression and Cognition

Abstract

Based in successful aging theory and terminal cognitive drop research, this paper investigates cerebrovascular burden (CVB), depressive symptoms and cognitive decline as threats to longevity. A subsample of stroke-free women over the age of 80 was identified in the Health and Retirement Survey (years 2000-2008). Mortality at 2, 6 and 8 year intervals was predicted using CVB (diabetes, heart disease, hypertension), depressive symptoms (Center for Epidemiological Studies Depression Scale) and cognitive decline (decline of 1 standard deviation or more on the 35-point Telephone Interview for Cognitive Status over 2 years). At most waves (2002, 2004, 2006) mortality was predicted by CVB, depressive symptoms and cognitive drop measured 2 years prior. CVB and depressive symptoms at the 2000 wave predicted mortality at 6 and 8-years. Older women with the greatest longevity had low CVB, robust cognitive functioning and few depression symptoms, supporting successful aging theory and terminal cognitive drop.

Introduction

Rowe and Kahn (1997) proposed criteria for successful aging comprised of avoidance of disease, maintenance of high cognitive and physical function, and sustained engagement in social and productive activities. This model grew from highly prolific MacArthur Foundation Study of Successful Aging, a \$10 million, 10-year research effort led by Rowe and Kahn. The objectives of this study, and the theoretical framework that grew from it, are to better understand risk factors for decline and to inform prevention efforts. For instance, work drawn from this initiative concluded that pulmonary health relates to both gross motor and cognitive functioning in late life, suggesting this as an area for primary intervention in preserving late-life independence (Cook et al., 1995). Drawing on the MacArthur Study data, Others have investigated modifiable risk factors for dementia, concluding that late-life depression may be a precursor of cognitive decline (Chodosh, Kado, Seeman, & Arun, 2007). Still other work based in this study found that older adults who frequently felt useful to others had lower rates of disability and mortality than less-engaged elders, emphasizing the importance of social engagement and productive activities (Greunewald, Karlamangla, Greendale, Singer, & Seeman, 2007). While support for this theory of successful aging has been mixed (Holstein & Minkler, 2003; Strawbridge, Wallhagen, & Cohen, 2002), it provides a useful framework for examining longevity. This paper will examine whether the Rowe and Kahn successful aging variables are each independently related to longevity. In the current paper we chose to examine this theory in older old women over 80 years. Women constitute a majority of all older adults over 80, but more importantly, they are more likely than men to experience disability and to live more years with disability than men (Arber & Cooper, 1999). Geriatric syndromes such as cardiovascular disease, cognitive decline and depression compromise functional independence more with increasing age (Rosso et al., 2011). Age 80 represents a point when medical treatment

planning for elders should be re-evaluated given the escalating risks associated with these comorbidities.

Behavioral factors as defined in this paper include psychological aspects of functioning that can be measured through self-report or performance-based assessment, such as mood and cognitive functioning (ie: depression and cognition). Important behavioral factors such as cognition and depression represent major risk factors for disability, often preceding disability (Bruce, Seeman, Merrill, & Blazer, 1994) and possibly reducing longevity. Serious disability, especially mobility loss, has been linked to reduced survival (Hirvensalo, Rantanen, & Heikkinen, 2000). Identifying behavioral factors that hasten disability onset may then lead to improved models of integrated care. Behavioral factors such as depression and cognitive decline may best be understood when integrated with chronic disease, especially those that enhance vascular risk.

Though Rowe and Kahn interpreted “avoidance of disease” broadly, vascular disease is particularly significant to healthy aging as these chronic conditions (e.g. hypertension, atrial fibrillation, diabetes) gradually compromise adaptive resources. Neural network functioning is broadly compromised by the effect of vascular disease on cerebral tissue, termed cerebrovascular burden (CVB). CVB is also associated with higher stroke risk, cardiac disease and sensorimotor impairment. Moreover, high CVB hastens the manifestation of clinically significant cognitive impairment, regardless of the specific etiology of cognitive decline (eg: normative aging, Alzheimer’s disease, Parkinson’s disease, vascular dementia) (Flicker, 2010). Elders with high CVB tend to have less prefrontal white matter volume, more white matter hyperintensities, and comparably impaired executive functioning (Raz et al., 2003). Considerable evidence also exists that CVB also contributes to the development of late-life depression symptoms (Coffey et al.,

1990; Sneed et al., 2008). Thus in addition to being a broad measure of physical health in the Rowe and Kahn model, inclusion of CVB will distinguish variance in mortality risk directly related to this variable, thereby providing a more stringent test of how depression and cognition independently relate to longevity.

Successful aging theory identifies sustained engagement in social and productive activities as central to healthy aging. Clinical depression throughout the lifespan is characterized by reduced enjoyment in activities and decreased social engagement. As such, depression symptoms in late life represent a significant barrier to successful aging based on this interpretation. Generally speaking, more depression symptoms translate to poorer health outcomes. For instance, people experiencing depression are at greater risk of a first heart attack (Glassman & Shapiro, 1998), stroke (Bos et al., 2008; Larson et al., 2001), cancer (Penninx, Buralnik, et al., 1998), worse health outcomes after controlling for cardiovascular risks (Glassman & Shapiro, 1998) and higher mortality (Arfken et al., 1999). Depression in later life was found to be a significant risk factor for death. Mehta et al (Mehta et al., 2003) reported that in a large sample of community-dwelling elders, mortality was significantly predicted by both number of depressive symptoms and performance on a measure of cognitive functioning. Similarly, it was reported that in a sample of older patients with debilitating or chronic medical diagnoses, after controlling for age, comorbidity and illness severity, functional impairment and cognitive functioning, depressed respondents were 34% more likely to die over three years (Covinsky et al., 1999). In a large (N=3065) Dutch sample of individuals between the ages of 55 and 80, depression was identified as a significant risk factor for death over four years. However the strength of this effect was partially eroded by the addition of other variables such as chronic disease, smoking and physical inactivity (Penninx, Geerlings, et al., 1999).

The third domain of successful aging theory identifies preservation of cognitive and physical functioning as critical to successful aging. Cognitive impairment limits quality of life by reducing the capacity for meaningful work and social interaction (Missotten et al., 2008), and rapid loss of cognitive faculties often suggests medical decline with a heightened mortality risk (Penninx, Geerlings, et al., 1999; Riegel & Riegel, 1972). Terminal cognitive drop is identified as an accelerated loss of cognitive functioning preceding death (Riegel & Riegel, 1972), by contrast to terminal decline which is a linear decline function preceding death (Palmore & Cleveland, 1976). A review from 2002 concluded that, largely because testing terminal drop theory requires a repeated-measures design, limited data existed supporting this theory (Bosworth & Siegler, 2002). Since this review several longitudinal studies have been published, including a recent study concluding that elders with sharp declines on the Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975), a brief cognitive screening measure, experienced more activity of daily living (ADL) disability and higher mortality rates than elders with more stable scores (Yaffe et al., 2010). While estimates of the temporal relationship between terminal drop and death vary, recent research identified evidence of terminal drop at a mean of 42 months before death (R. S. Wilson et al., 2007) in a large sample of dementia-free elders. These estimates are roughly similar to the original estimates of about 5 years reported by Riegel et al (1972). Similarly, past work drawing on the Health and Retirement Survey (HRS) data identified a relationship between cognitive impairment and mortality over a 2-year interval (Langa et al., 2008); however, this study evaluated cognitive decline cross-sectionally and did not include other markers of decline such as CVB or depression. Of note, Langa et al reported evidence of compression of cognitive morbidity; elders with moderate or severe cognitive

impairment in 2002 had greater risk of death over 2 years than those with similar levels of impairment in 1993.

Comorbid cognitive impairment and depressive symptoms suggest particularly high risk of death (Arfken et al., 1999; Mehta et al., 2003); however, these studies evaluated cognitive functioning cross-sectionally. While impairment on cognition measures *suggests* decline from demographically-representative norms, the concept of terminal cognitive drop specifies rapid loss of cognitive functioning over a brief period of time. Relatively few studies relating cognition and longevity evaluate how decline over brief periods relates to longevity, and even fewer investigate whether depression and cognitive decline are independent predictors of mortality. Because cognition and mood, domains in which impairment may be most evident to family and medical practitioners alike, tend to be interrelated in late life (Bielak, Gerstorf, Kiely, Anstey, & Luszcz, In Press; Mast, Yochim, et al., 2004), it is important to distinguish the individual relationships of these variables with longevity.

Objectives of the Present Study

This investigation seeks to examine whether all three domains of Rowe and Kahn's successful aging paradigm independently predict longevity in a large sample of stroke-free women over the age of 80. In particular, this study emphasizes two behavioral domains that are of particular relevance in clinical settings – depression and cognitive decline. This theoretical orientation, based on a broad reading of the literature, posits that elders with few depression symptoms and preserved cognitive functioning will experience greater longevity. In addition to CVB, other health variables such as self rated health and Body Mass Index (BMI) will be included in order to control for general health. The model proposed predicts that both depression and cognitive decline will predict mortality in this sample. Hypothesis 1 looks at survival across

the entire study period of 8 years, whereas hypothesis 2 examines proximate predictors of death across 2-year intervals.

Hypothesis 1: Physical health, depressive symptoms and cognitive decline at baseline (2000 wave) will all be independent predictors of longevity conceptualized as survival across the entire 8-year study period.

Hypothesis 2: Incidence of death at each wave (2002, 2004, 2006 and 2008) will be predicted by CVB, cognitive decline and depressive symptoms at the previous wave.

Method

Sample

The Health and Retirement Survey (HRS) is a prospective cohort study conducted by the University of Michigan with support from the National Institute on Aging. The first wave of the HRS occurred in 1992 with a 51 to 61 year-old cohort and was merged with the older (70 years and older) Asset and Health Dynamics of the Oldest Old Study (AHEAD) cohort in 1998. Two additional cohorts were added in 1998 to fill in the gaps between these two groups. Briefly, the HRS is a multistage probability cohort sample of U.S. households. Further details on the HRS design and methods have been previously published (Heeringa & Conner, 1995).

The present study utilized the Health and Retirement Survey (HRS) that was prepared by the RAND Center for the Study of Aging (RAND HRS). The selected portion of this publically-available, longitudinal dataset includes five waves at two year intervals from 2000 through 2008 (waves 5 through 9). Inclusion criteria included age over 80 years at the first wave and female sex. This study made use of the 1998 TICS score to identify incidence of cognitive decline from 1998 to 2000. Because stroke is associated with highly variable cognitive performance, participants with history of stroke prior to 1998 were excluded. Respondents who were unable to

complete survey materials at the 1998 data collection were also excluded as missing data would have precluded calculation of 1998-2000 cognitive change scores. This data set is demographically representative of the female US population over age 80.

Measures

Medical Data

Medical data (hypertension, diabetes, history of heart disease, height, weight) and lifetime history of smoking was collected by self-report. CVB was identified as the number of cerebrovascular risk factors (hypertension, diabetes, history of heart disease) reported creating a score ranging from 0 to 3.

Depressive Symptoms

A shortened, 8-item form of the original Center for Epidemiological Studies Depression Scale (CESD) was used to evaluate depression (Radloff, 1977). Six of the eight items are negatively worded and two are positively worded. Participants are asked to respond “yes” or “no” to each item (‘was depressed,’ ‘everything was an effort,’ ‘sleep was restless,’ ‘was happy,’ ‘felt lonely,’ ‘enjoyed life,’ ‘felt sad,’ ‘could not get going’) that occurred within the preceding week. Scores ranged from 0 to 8 with higher scores indicating greater depressive symptoms. Using HRS data, the reliability of the 8-item CESD measure was adequate, with Cronbach’s alpha ranging from .81 to .83 between waves (Steffick, 2000). High validity, and symptom dimensions similar to those in the longer 20-item CESD have been demonstrated using these 8 items (Steffick, 2000; Wallace et al., 2000). The CESD is broadly used in the epidemiological study of late-life depression (Beekman et al., 1997). While the CESD literature describes a clinical cutoff that can be used to distinguish respondents with probable depression (Steffick,

2000), this measure was used as a semi-continuous variable representing the full range depressive symptoms in this population sample .

Cognitive Functioning

The HRS data includes a brief standardized 35-point measure of cognitive functioning that was developed for remote screening of cognitive disorders based on the Telephone Interview for Cognitive Status (Brandt et al., 1988). It includes indices of orientation, concentration, short-term memory, mathematical skills, praxis and language and has a maximum score of 35 points (observed range: 0-35) with higher scores reflecting better functioning . This instrument has a Cronbach's alpha of .69 and past work has identified factors reflecting mental status and memory(Herzog & Wallace, 1997). The TICS has demonstrated high test-retest reliability and is generally sensitive to cognitive impairment (Brandt et al., 1988; Desmond et al., 1994; Järvenpää et al., 2002; Welsh et al., 1993). For all of the following models cognitive decline was identified as a decrease in TICS score from one wave to the next wave of more than one standard deviation (6.1 points) based on baseline data.

Self-Rated Health

Self-rated health change was measured with a single question assessing the respondents' perception of change in health since the last data collection 2 years prior. Change in self-rated health was assessed with the question, "Compared to your health when we talked with you in [last wave] would you say that your health is better now, about the same, or worse?" Response options included "much better," "somewhat better," "same," "somewhat worse," "much worse," comprising a 5-point scale. This variable was included as a semi-continuous measure.

Statistical Methodology

Binary logistic regression was performed to model the likelihood of death between baseline (2000) and either 2006 or 2008 as a function of demographics, cognitive function, CVB and depression. While the study spans the years 2000-2008, the logistic regression using 2006 as an end-point was included as closer to half the sample had died at this wave, thereby optimizing the statistical power of the model. Variables were entered blockwise with age, years of education, and body mass index (BMI) entered in the first block. The second block included CVB as reported in the 2000 wave. The third block included the self-rated health change variable at the 2000 wave. The fourth block included CESD score at the 2000 wave and a variable reflecting incidence of decline greater than 1 standard deviation (>6 points) on the TICS between the 1998 and 2000 waves.

To better track the relationship between TICS score decline, mood and longevity over the course of the study, four additional logistic regression models were computed. In the first, incidence of death in 2002 was predicted using 2000 CVB, the 2000 CESD score and the index reflecting a drop in TICS score between 1998 and 2000 exceeding 1 standard deviation. The second model predicted death in 2004 based on CVB in 2002, CESD score in 2002 and incidence of decline in TICS score of more than 1 standard deviation between 2000 and 2002. The third and fourth models predicted death in 2006 and 2008 using similar predictors, respectively.

Results

Of the 1368 respondents who met criteria at the 1998 wave, 1186 were living at the 2000 wave. Of these, 417 were living at the 2008 wave representing a 64.8% mortality rate over this 8 year period. The sample at the 2000 wave is described in Table 3.1. The mean age was 85.6

years ($SD=3.8$). On average, respondents had 11 years of formal education ($SD=3.4$). The mean BMI at baseline was 24.4 ($SD=4.9$). The average number of cerebrovascular risk factors reported was 1 ($SD=0.8$). The mean CESD score was 2.1 ($SD=2$) suggesting a low rate of depressive symptoms in this population. The mean score on the 35 TICS measure was 18.1 ($SD=5.9$).

As can be seen in table 3.2, CVB and depressive symptoms were significant predictors of mortality between 2000 and 2006. In addition, age, and BMI were also significant predictors. Cognitive decline and self-rated health showed a trend toward being significant predictors. A slightly different picture emerged with respect to 2008 outcomes. CVB was a significant predictor of mortality, and again BMI and age also predicted mortality. Depressive symptoms showed a trend toward significance while self-rated health was not a significant predictor. Cognitive decline between 1998 and 2000 was not a significant predictor of mortality at the 2008 wave. Overall, the logistic regressions over 6 and 8 years provided partial support for applying Rowe and Kahn's successful aging model to longevity.

Shown in Table 3.3, four additional logistic regressions predicting death in 2002, 2004, 2006 and 2008 were completed to better understand the relationship between CVB, mood, cognitive change and longevity over brief periods of time. CESD and TICS scores are unavailable for many participants, primarily for reasons of incapacity. As a result of listwise deletion caused by absent data on these predictor variables, these four logistic regression analyses included 69% (2002), 61% (2004), 54% (2006), and 43% (2008) of respondents who died, respectively. As described in Table 3, CVB significantly predicted mortality in the 2002, 2004 and 2008 waves. CESD score was a significant predictor of death in the 2002 and 2004 waves. Decline in TICS score over 2 years of more than 1 standard deviation significantly

predicted incidence of death in 2004 and 2008 and showed a trend toward significance in 2002 ($p=.088$).

Discussion

The primary findings of the present research are that, among women over the age of 80, CVB, depressive symptoms and rapid cognitive decline (terminal drop) predict incidence of mortality over brief periods (2 years). CVB significantly predicted 2-year mortality at 3 of 4 waves, and depressive symptoms and cognitive decline significantly predicted mortality at 2 of 4 waves. Over long periods (6 or 8 years) mortality was significantly predicted by age, BMI, and CVB. Additionally, depressive symptoms significantly predicted mortality over 6 years and showed a trend toward significance in predicting mortality over 8 years. Incidence of rapid cognitive decline was not a significant predictor of death over 6 or 8 years. As demonstrated in the analyses predicting death over 2-year periods, rapid cognitive decline is a robust predictor of proximal death. Together, these findings suggest that in addition to undermining quality of life and independence as described by Rowe and Kahn, sharp cognitive decline suggests high risk of imminent death. Cognitive drop, even in the older old is a significant indicator of declining health and potentially shortened life. While it is well documented that cognitive abilities decline in those over 80 (Dahle, Jacobs, & Raz, 2009), it is when declines are significantly above the norm when life expectancy is affected among the older old. By contrast, many of those who died toward the end of this study had robust cognitive functioning at this baseline interval. These results are consistent with past work describing the relationship between CVB, mood, cognitive decline, and longevity (Arfken et al., 1999; Mehta et al., 2003; Penninx, Geerlings, et al., 1999; Riegel & Riegel, 1972; R. S. Wilson et al., 2007; Yaffe et al., 2010).

The present findings support and extend Rowe and Kahn's (1997) successful aging theory by relating low CVB, relatively few depressive symptoms and preserved cognitive functioning, representing the three domains of successful aging theory, to greater longevity in this sample of older women. In the present study, Rowe and Kahn's formulation of successful aging is expanded from quality of life to length of life. Heightened depression and rapid loss of cognition were significantly related to timing of death, and conversely robust functioning was related to longevity. These findings underscore the significance of behavioral factors to the discussion of longevity. Behavioral factors such as mood and gross cognitive functioning are basic characteristics of the individual patient, and these findings highlight the importance of subjective reports or clinician perceptions of decline in these areas, especially when working with older patients. The finding that CVB predicts longevity broadly supports the large medical and epidemiological literature citing conditions such as heart disease, hypertension and diabetes as risk factors for death (discussed in Flicker, 2010). Our finding that depressive symptoms predict longevity corroborate significant past work on this subject (Arfken et al., 1999; Covinsky et al., 1999; Mehta et al., 2003; Penninx, Geerlings, et al., 1999).

These findings are also consistent with the concept of terminal cognitive drop (Riegel & Riegel, 1972). While some studies support the terminal cognitive decline effect over longer periods of time (Riegel & Riegel, 1972; R. S. Wilson et al., 2007; Yaffe et al., 2010), these findings support other research (Arfken et al., 1999; Mehta et al., 2003) that terminal cognitive drop theory can be applied over brief periods of time. Additionally, most research supporting terminal cognitive decline relates mortality to impaired performance on cognitive measures, suggesting decline from an idiographic baseline and consequently discounting the time period

over which decline occurs. By contrast, the present study contributes to the existing literature by testing this theory among older-old women using longitudinal data.

The primary limitation of the present study is that cognitive and mood data are not available for many respondents nearing death. This data is absent largely for reasons of incapacity. Consequently, it is likely that the relationship between depressive symptoms, cognitive decline and longevity is underrepresented by the present research. Another limitation is the use of categorical self-reported CVB data. However, use of such data is common in population-based samples and reasonable concordance values between self-reports of disease and medical chart reviews have been reported (Bush et al., 1989; Psaty et al., 1995). Future research should build on the present finding by identifying relationships between markers of cerebrovascular health, depression and cognitive decline.

CHAPTER 4

Vascular Depression: An Early Warning Sign of Frailty

Abstract

Objectives: Frailty is a common geriatric disorder associated with ADL impairment, hospitalization, and death. Phenomenological evidence suggests that late-life depression (Katz, 2004), particularly vascular depression, may be a risk factor for frailty and this study tests that hypothesis.

Methods: We identified a sample of stroke-free women over the age of 80 from the Health and Retirement Survey. Frail respondents experienced at least three of the following: wasting, exhaustion, weakness, slowness, and falls. Respondents with vascular depression had both high cerebrovascular burden (at least two cerebrovascular risk factors) and depression, (score ≥ 3 on the 8-item CESD).

Results: At baseline, the prevalence of frailty was 31.5%. Over a 4-years the incidence of frailty was 31.8%. After controlling for age, education, ADL and IADL functioning, arthritis, pulmonary disorders, cancer, and self-rated health, vascular depression significantly predicted new cases of frailty.

Discussion: These findings suggest that vascular depression is a prodrome for frailty.

Key Words: Frailty, Vascular Depression, Older Women

Introduction

Research on frailty among older adults has increased over the past decade, both to define phenotypes and identify markers for future frailty (Fried et al., 2001; Varadhan et al., 2009). Frailty is clearly related to advanced age, heart dysfunction (Varadhan et al., 2009), subclinical vascular biomarkers (Newman et al., 2011), and being female (Fried et al., 2001). The clinical pathways that lead to frailty are poorly understood; our study attempts to increase knowledge of the underlying mechanisms of this common late-life syndrome by examining a specific pattern of medical comorbidity—vascular depression—and incorporating it into a model of other medical conditions and functional abilities to predict new-onset frailty cases in women over the age of 80.

The co-occurrence of vascular diseases and depression may signal that if elders are treated by standard means, they will decline into frailty (Rosso et al., 2011), a syndrome that imposes a significant burden on the health-care system (Fassbender, Fainsinger, Carson, & Finegan, 2009). While frailty, comorbidity, and disability are distinct concepts (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004), this study aims to increase our understanding of how vascular depression—which is a combination of particular medical comorbidities—and reported disability affect the incidence of frailty in older-old women.

Frailty

Frailty is conceptualized as the combined effects of life stress that result in multisystemic dysregulation of homeostatic systems (Clegg, 2011; Fried et al., 2004). Although there are multiple models of frailty, Fried's (Fried et al., 2001) continues to be among the foremost (Clegg, 2011). In this model, frail individuals are described as having at least three of the following conditions: unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity. Fried (2001) reported that frailty is more common among women, Black elders, and those with lower education and income, relatively poor health, and greater medical

comorbidity and disability. Frailty grows more common with increasing age; base rates range from 3% to 7% of individuals between ages 65 and 75 (Fried, 2003), and more than 30% for individuals in their 90s (Walston et al., 2002). Frailty is also associated with comparably poor subjective health evaluations, vascular disease (Barzilay et al., 2007; Fried et al., 2001), arthritis (Fried et al., 2001), greater heart rate variability (Varadhan et al., 2009), and insulin resistance (Barzilay et al., 2007). Frail individuals experience decreased mobility and higher rates of impairment in performing activities of daily living (ADLs), hospitalization, and death (Fried et al., 2001; Lupon et al., 2008), making this syndrome a significant public health concern.

Depression

Vascular depression is defined as the increased prevalence of depression symptoms in late life resulting from high cerebrovascular burden (CVB; Alexopoulos et al., 1997a). The vascular depression hypothesis has generated two complementary lines of research, both of which inform this discussion of vascular depression and frailty. One uses neuroradiological data to describe the relationship between prefrontal subcortical white matter hyperintensities, which are typically attributed to CVB, and late-life depression symptoms (Sneed et al., 2008). Other studies, however, have reported no significant relationship between cerebral vascular change and depression (Rainer et al., 2006). The second line of research approaches the relationship from a clinical perspective, relating the presence of multiple cerebrovascular risk factors (diabetes, hypertension, etc.) to development of depression symptoms in late life (Mast et al., 2008). This conceptualization of vascular depression is also not universally supported (Lyness et al., 1999). Nonetheless, both areas of vascular depression research generally support Alexopoulos's hypothesis that affective functioning involves an elaborate network of fronto-striatal projections

(Drevets et al., 2008) and appears to be highly sensitive to microvascular insult (Sneed et al., 2008).

Katz (2004) discussed the numerous theoretical and phenomenological connections between depression and varying models of frailty. He noted that white matter disease characterizes both late-onset depression and psychomotor deficits, which can be symptomatic of frailty. Katz did not, however, speculate as to whether vascular depression, as opposed to late-life depression, is related to frailty. Andrew and Rockwood (2007) reported that psychiatric disease is four times more common among frail elders than among the most robust elders. Interpretation of these results is limited, however, by the use of cross-sectional data and the identification of psychiatric illness based on retrospective self-report. Additionally, this study included CVB markers (hypertension, cardiac disease, and diabetes) as indicators of frailty, precluding analysis of these variables as risk factors *for* frailty. Other work has related depression to various correlates and indicators of frailty, including fall risk (P. Thomas et al., 2009) malnutrition (P. Thomas et al., 2009) which can lead to wasting, steep decline in strength (Rantanen et al., 2000), and deficits in ADL functioning and mobility (Penninx, Leveille, et al., 1999).

Vascular Depression and Disability as an Early Indicator of Frailty

In this study, vascular depression was conceptualized as a prodrome for frailty. As described above, vascular depression has a neurological basis. Katz (2004) theorizes that cerebrovascular disease that causes prefrontal white-matter hyperintensities and vascular depression may also lead to posterior white matter hyperintensities, resulting in characteristics of frailty such as falls, slowness, and weakness. Recent findings of higher rates of cardiovascular disease and cerebral infarcts among frail elders support this hypothesis (Newman et al., 2011).

Accordingly, vascular depression may be a highly sensitive, clinically relevant indicator of global cerebral disease process and, in turn, a harbinger of subsequent frailty and mortality. However, this hypothesis has not been explicitly tested; neither Katz (2004) nor Newman (2011) examined whether vascular depression was a better predictor of frailty onset than either vascular disease without depression or depression without vascular disease.

The objectives of this study were to (1) describe the prevalence of frailty in a sample of stroke-free women over the age of 80 and the incidence of new cases of frailty over 4 years, and (2) to test the hypothesis that vascular depression and disability predict frailty among older-old women. This study sought to examine whether vascular depression and disability predicted new-onset frailty. To examine the specificity of vascular depression, we included as control variables other medical conditions (arthritis, pulmonary disease, and cancer) that are often related to disability.

Method

Sample

The Health and Retirement Survey (HRS) is an ongoing prospective multistage probability cohort study of U.S. households conducted by the University of Michigan with support from the National Institute on Aging (Heeringa & Conner, 1995). The first wave of the HRS occurred in 1992, with a 51- to 61-year-old cohort, and in 1998 was merged with the 70-and-older cohort of the Asset and Health Dynamics of the Oldest Old Study. Also in 1998, two additional cohorts were added to fill the gap between the two groups.

Our study included HRS data drawn from the 1998 wave, when many participants were added to the study. This sample included female respondents without history of stroke in 1998. Respondents were excluded if they were unable to independently complete survey materials

(e.g., the CES-D, a measure of depressive symptoms) at the 2000 wave. This data set was otherwise demographically representative of the female U.S. population over age 80 and included 1139 respondents. Complete frailty data was available at 2000 and 2004, so we included data drawn from these waves (waves 5 and 7) exclusively.

Measures

Frailty

We measured frailty using Fried's (2001) conceptualization of frailty as a phenotype. Due to differences between the HRS data and Fried's model of frailty, we adapted the frailty index to include five symptoms: wasting, weakness, slowness, fatigue or exhaustion, and falls. The wasting criterion was met if a respondent reported loss of at least 10% of body weight over a 2-year period. The weakness criterion was met if they endorsed the question, "Because of health problems, do you have any difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries?" The slowness criterion was met if respondents answered in the affirmative to the question, "Because of a health problem, do you have any difficulty with getting up from a chair after sitting for long periods?" The fatigue or exhaustion criterion was met if the respondent answered in the affirmative to the question, "Since we last talked with you in [the last wave], have you had any of the following persistent or troublesome problems: . . . severe fatigue or exhaustion?" The falls criterion was met if the respondent answered in the affirmative to the question, "Have you fallen down in the past 2 years?" While Fried's criteria include low energy expenditure, this variable was not available in the HRS data. Instead, the frailty phenotype was modified to include falls, which was found to be an indirect measure of energy expenditure (Montero-Odasso et al., 2011). None of these frailty items was drawn from the CES-D. Individuals who met at least three of the criteria were identified as frail.

Self-Reported Medical Conditions

Medical data (hypertension, diabetes, history of heart disease, arthritis, pulmonary disorders, cancer) and lifetime history of smoking were collected by self-report. Consistent with past work (Mast, Neufeld, et al., 2004; Mast, Yochim, et al., 2004; Yochim et al., 2003), respondents with high CVB were those with two or more cerebrovascular risk factors (hypertension, diabetes, cardiac disease, and history of smoking). Hypercholesterolemia was not included because it was not reported in the data at every wave.

Functional Independence

The score for ADLs reflected how many of the following activities the respondent reported requiring assistance with: bathing, eating, dressing, walking across a room, and getting in or out of bed. Scores ranged from 0 to 5. Instrumental activities of daily living (IADLs) were measured by identifying which of the following the respondent required assistance with: using a telephone, taking medication, and handling money. Scores ranged from 0 to 3.

Self-Rated Health

Change in self-rated health was assessed with the question, “Compared to your health when we talked with you in [last wave], would you say that your health is better now, about the same, or worse?” Response options were “much better,” “somewhat better,” “same,” “somewhat worse,” and “much worse,” comprising a 5-point scale.

Depressive Symptoms

A shortened, 8-item form of the original Center for Epidemiological Studies Depression Scale (CES-D) was used to evaluate depression (Radloff, 1977). Six of the eight items are negatively worded and two are positively worded. Participants are asked to respond “yes” or “no” to each item (“was depressed,” “everything was an effort,” “sleep was restless,” “was

happy,” “felt lonely,” “enjoyed life,” “felt sad,” “could not get going”), based on whether or not they had experienced it during the preceding week. Scores ranged from 0 to 8, with higher scores indicating greater depressive symptoms. Using HRS data, the reliability of the 8-item CES-D measure was adequate, with high Cronbach’s alpha (.81-.83; (Steffick, 2000). The 8-item CES-D has high internal consistency ($\alpha = .77$) and validity (Steffick, 2000) and is broadly used in epidemiological studies of late-life depression (Beekman et al., 1997). Citing the recommended interpretation of this measure (Steffick, 2000), CES-D scores ≥ 3 were interpreted to indicate probable clinical depression.

Statistical Methodology

A variable representing clinically defined vascular depression was created in which respondents with *neither* high CVB nor probable depression were assigned a score of 0, respondents with *either* high CVB or probable depression were assigned a score of 1, and respondents with *both* high CVB *and* probable depression were assigned a score of 2. Complete frailty data were reported in the 2000 and 2004 waves. Data in the 2000 wave were used to assess how variables of interest predicted the prevalence of frailty at baseline among all available respondents. How these variables predicted the incidence of new frailty in 2004 was assessed by excluding respondents who were frail at the 2000 wave.

Two chi-square tests of independence were completed that examined the prevalence of frailty at 2000 and the incidence of new frailty in 2004, using vascular depression as the single predictor. A step-wise logistic regression was then performed to evaluate how demographic variables (age, years of education), ADLs, IADLs, arthritis, pulmonary disorders, cancer, change in self-rated health, and vascular depression (measured in 2000) predicted the prevalence of

frailty in 2000. A second step-wise logistic regression was then performed to test how these indicators predicted incidence of new frailty in 2004.

Results

Of 1139 respondents living at the 2000 data collection, 992 respondents completed baseline survey materials at the 2000 baseline, and complete data were available for 984 of these respondents. These 984 respondents were included in the logistic regression predicting prevalence of frailty described below. Of these, 310 were frail in 2000 (prevalence = 31.5%) and were excluded from the second logistic regression model that predicted incidence of frailty. Of the remaining 674 respondents, 491 were still living in 2004 and complete data were available for 459 respondents. The second logistic regression included these 459 respondents. As shown in Table 4.1, the sample had a mean age at baseline (year 2000) of 84.53 years ($SD=3.03$) and 11.24 mean years of education ($SD=3.13$). The sample was predominantly White, and most respondents remained independent at baseline, as suggested by the relatively low levels of ADL and IALD impairment. Of the 984 respondents included in the 2000 prevalence analysis, 32.8% had CES-D scores of at least 3—suggesting probable depression—and the mean CES-D score was 2.07 ($SD=1.98$). Of the 459 respondents included in the 2004 incidence analysis, 22% had CES-D scores at the 2000 data collection that suggested probable depression; the mean 2000 CESD score was 1.55 ($SD=1.70$).

Over the 4-year course of the study, the incidence of frailty was 31.8% ($n = 146$). Table 4.2 displays prevalence rates in 2000 (all available respondents who met inclusion criteria) and frailty incidence rates in 2004 (excluding any respondents who were frail in 2000) among respondents at each level of the vascular depression variable. As can be seen in the Table frailty was most common among those with vascular depression. Indeed when compared to those with

either depression alone or vascular burden alone those with vascular depression were significantly more likely to be frail, both at baseline ($X^2=13.59$, $p<.001$) and four years later ($X^2=5.77$, $p=.02$). Interestingly, those with either depression or vascular burden were more likely than those without either to be frail both at baseline ($X^2=22.49$, $p<.001$) and four years later ($X^2=5.55$, $p=.02$).

Results of the first step-wise logistic regression describing frailty prevalence in 2000 are displayed in Table 4.3. At the 2000 wave, 31.5% of the sample was identified as frail. Age, education, ADLs, IADLs, arthritis, pulmonary disorders, cancer, and self-reported health change in 2000 were included in the first step of the model. In this first step, frailty was significantly predicted by age ($\beta=.06$, $Wald=9.11$, $p=.003$), ADLs ($\beta=.641$, $Wald=57.89$, $p<.001$), arthritis ($\beta=1.09$, $Wald=30.47$, $p<.001$), and change in self-rated health ($\beta=.46$, $Wald=20.91$, $p<.001$). The addition of the vascular depression variable substantively improved the model ($X^2=13.29$, $p<.001$). In the final prevalence model, frailty was significantly predicted by age ($\beta=.06$, $Wald=9.52$, $p=.002$), ADL disability ($\beta=.60$, $Wald=49.61$, $p<.001$), arthritis ($\beta=1.05$, $Wald=28.18$, $p<.001$), self-rated health change ($\beta=.39$, $Wald=14.58$, $p=.001$), and vascular depression ($\beta=.41$, $Wald=26.68$, $p<.001$). This model had a sensitivity of .445 and specificity of .914. Positive predictive value (PPV) was .704 and negative predictive value (NPV) was .782. The incremental validity using the PPV was .389 and .097 using the NPV.

Results of the second step-wise logistic regression describing frailty incidence in 2004 are displayed in Table 4.4. Variables were entered in the same manner as the first logistic regression. In the first step of the logistic regression, only ADLs ($\beta=.50$, $Wald=7.85$, $p\leq.01$) and self-reported health change ($\beta=.69$, $Wald=15.89$, $p\leq.001$) significantly predicted incidence of frailty in 2004. In the second step, the addition of the vascular depression variable significantly

improved the overall model ($X^2=9.14$, $p=.003$). In this final model, ADLs ($\beta=.49$, Wald=7.21, $p\leq.01$), self-rated health change ($\beta=.65$, Wald=13.53, $p\leq.001$), and vascular depression ($\beta=.49$, Wald=9.12, $p\leq.01$) emerged as significant predictors of frailty in 2004. This second model had low sensitivity (.27) but high specificity (.95), and both good PPV (.70) and NPV (.74). This model had incremental validity of .384 using the PPV and .054 using the NPV.

Discussion

Our first finding is that the prevalence of frailty in this demographically representative sample of stroke-free women over the age of 80 was 31.5%. Of the respondents who were not frail at baseline, the incidence of frailty after 4 years was 31.8%. The second finding was that vascular depression—characterized as the co-occurrence of high CVB and clinically significant depression symptoms—predicted prevalent and incident frailty in a sample of women over 80. Importantly, those with vascular depression had higher rates of frailty than either those with depression alone or vascular burden alone. The prevalence and incidence estimates are generally consistent with other estimates of frailty frequency in this demographic (Affairs, 1990; Walston et al., 2002). Katz predicted that depression precedes frailty in late life (Katz, 2004). The findings of the current study support this hypothesis and build on Katz's work by demonstrating that a specific subtype of depression (i.e., vascular depression) is a better predictor of new-onset frailty.

In addition to vascular depression, ADL disability was a significant predictor of frailty onset. Fried et al. (Fried et al., 2004) distinguished the concepts of comorbidity, disability, and frailty, while noting that in aging populations, these syndromes often overlap. The present findings support this conceptualization, and extend the model by suggesting that certain

combinations of comorbidity and disability have a temporal ordering with frailty. For instance, frailty was extremely uncommon among those without ADL disability and vascular depression.

The primary limitation of the study is the use of self-reported health data and lack of clinical evaluations for depression. However, this practice is common in population-based samples, and adequate agreement between self-reports of disease and medical chart reviews has been reported (Bush et al., 1989; Psaty et al., 1995). A second limitation of this analysis is that the high rate of mortality in this sample resulted in listwise deletion of the most medically vulnerable elders. Consequently, it is probable that these findings underestimate the strength of the relationship between disability, vascular depression, and frailty. Future research may explore how vascular depression and frailty relate to longevity among the older-old.

The findings of this study significantly extend our understanding of the impact of vascular depression as a pathway to frailty. As medical practice with older patients trends toward collaborative care, depression is emerging as a critical clinical indicator of decline in medical functioning. While vascular depression is conceptualized as having a neurological basis, some have described empirically supported interventions for this syndrome (Alexopoulos et al., 2011; Mackin & Arean, 2005), suggesting that vascular depression may be a modifiable risk factor for frailty, even in late life. Other interventions suggested by these findings include addressing CVD much earlier, thereby reducing the deleterious effects of hypertension, diabetes, and cardiac disease.

CHAPTER 5

Vascular Depression and Frailty: A compound threat to longevity among older-old women

Abstract

Vascular depression theory posits that high cerebrovascular burden predisposes, precipitates and perpetuates development of depression symptoms in late life (Alexopoulos et al., 1997b). Building on past work suggesting that vascular depression is a prodrome for frailty (Paulson & Lichtenberg, 2011), this paper tests a theoretical framework that vascular depression symptoms are an early marker of a broader pattern of decline characterized by more frailty symptoms and shortened lifespan. The specific hypothesis tested in this model is that depression predicts mortality through frailty. A 5-level vascular depression variable was based on CES-D scores and number of cerebrovascular risk factors. Frailty was measured as a semi-continuous variable based wasting, slowness, weakness, fatigue and falls (score 0-6). Vascular depression and frailty symptoms were modeled using slope and intercept terms. Mortality was modeled using a discrete-time survival term. The data supported the proposed model ($RMSEA=.051$; $CFI=.971$; $X^2=429.27$, $p<.001$). Higher vascular depression symptom slope predicted higher frailty symptom slope ($\beta=.23$, $p=.02$). Higher vascular depression intercept values significantly predicted higher frailty intercept term values ($\beta=.42$, $p<.001$), which predicted probability of mortality ($\beta=.07$, $p=.04$). Additionally, vascular depression symptoms significantly predicted mortality through frailty symptoms ($\beta=.03$, $p=.04$). Our results support the proposed theoretical framework and suggest that vascular depression symptoms are associated with a clinical trajectory including more frailty symptoms and shorted remaining lifespan. This finding supports integrated care for geriatric patients and suggests specific targets for intervention with older patients experiencing vascular depression symptoms.

Introduction

Up to 30% of elders die with, or because of, frailty (Fassbender et al., 2009; Paulson & Lichtenberg, 2011) and frail elders' need for prolonged long-term care makes this syndrome among the most costly causes of death (Fassbender et al., 2009). The growing literature on frailty identifies this syndrome as a marker of functional decline, physiological dysregulation, and heightened mortality risk (Fried et al., 2001; Varadhan et al., 2009). The recent trend toward collaborative care and treatment of medical syndromes is associated with improved patient outcomes (Boult et al., 2008), greater satisfaction for medical professionals (Sylvia et al., 2008), and reduced health-care costs (Brownlee, 2007; Sylvia et al., 2008), especially for vulnerable aging patient populations. Women constitute a growing majority of adults over age 80 and live more years with disability than do men. Improving our understanding of broad patterns of decline and preserving independence, especially in this at-risk population, is a priority in our national efforts to optimize use of healthcare resources.

We evaluated a theoretical framework that relates the symptoms of vascular depression, frailty, and earlier mortality to better understand the pathways that lead to frailty among older-old women. Our objectives were to describe the temporal relationship and connections between vascular depression symptoms, frailty symptoms, and mortality in a sample of stroke-free women over the age of 80.

In the proposed model, high cerebrovascular burden (CVB), which is characterized by disorders such as hypertension, diabetes, and cardiac disease, is viewed as a threat to long-term adaptive functioning. For example, even healthy adults with high CVB have smaller prefrontal cortex and white matter volumes and more white matter hyperintensities (Raz et al., 2003). High CVB hastens the presentation of cognitive impairment resulting from all causes (Flicker, 2010).

Older adults with high CVB also demonstrate exaggerated age-related declines in domains such as psychomotor speed and working memory (Dahle et al., 2009). Elders with high CVB and concomitant white matter hyperintensities are also at greater risk for mood decline, termed vascular depression (Coffey et al., 1990; Sneed et al., 2008).

Vascular depression theory (Alexopoulos et al., 1997b) posits that high CVB compromises neurological functioning and that, as a result, depression symptoms develop. Consistent with vascular depression theory, depressed elders are more likely to have prefrontal white matter hyperintensities (Coffey et al., 1990; Sneed et al., 2008) and relatively impaired cognitive functioning on measures of executive functioning (Mast, Yochim, et al., 2004). Vascular depression theory has produced two complementary lines of research. One describes how CVB-mediated neurological changes—and prefrontal white matter hyperintensities in particular—predict higher rates of depression among elders (Sneed et al., 2008). The other describes clinically defined vascular depression, in which greater depression symptoms are predicted by comorbidities such as diabetes, hypertension, and cardiac disease (Mast, Neufeld, et al., 2004; Yochim et al., 2003). While results have been mixed for both neuroradiological (Rainer et al., 2006) and clinical research (Lyness et al., 1999), both approaches generally support vascular depression theory. Of particular relevance to this synthesis, elders with high CVB and depression have much higher mortality rates than their healthier counterparts (Lavretsky et al., 2010).

The proposed model hypothesizes that vascular depression symptomatology is one entry point into the cycle of frailty. Broadly speaking, frailty symptoms can be viewed as the combined effects of life stress that results in multisystemic dysregulation of homeostatic systems (Clegg, 2011; Fried et al., 2004). Numerous models of frailty exist, including Fried's

specification of wasting, weakness, slowness, fatigue, and low activity. We chose this model, which is commonly used in the literature, for this study. Fried (2001) reported that frailty is more common among women, Black elders, medically compromised individuals, those with disabilities, and those with lower education and income, and becomes increasingly prevalent in late life. As described by Katz (2004), both late-life depression and frailty are characterized by white matter hyperintensities, in addition to other numerous phenomenological and theoretical similarities.

Recent work by our group has shown that vascular depression symptoms can be an early warning sign of frailty (Paulson & Lichtenberg, 2011). Although both vascular depression and frailty symptoms have been associated with heightened mortality rates (Cawthon et al., 2007; Fried et al., 2001), the model we propose posits that vascular depression symptoms are an earlier indicator of a broader pattern of decline that is subsequently characterized by higher rates of frailty symptoms and mortality. Cerebrovascular risk factors place an enormous burden on the physical—and especially the neurological—integrity of the oldest old. In our proposed model, vascular depression symptoms are an early indicator of the decline of brain integrity, with frailty symptoms emerging later as neurological damage continues to accrue.

The proposed model describes a dynamic process that develops over a period of years. Accordingly, detection of these effects requires a longitudinal research design that uses large-scale cohort panel data, such as the Health and Retirement Study (HRS). The hypothesis tested in this paper posits that vascular depression will predict frailty, and will predict mortality indirectly through frailty in a sample of stroke-free women over the age of 80.

Method

Sample

The HRS is a National Institute on Aging–supported prospective, multistage cohort study of U.S. households (Heeringa & Conner, 1995). The HRS data includes four smaller samples consisting of (a) respondents from the original (1992) HRS who were aged between 51 and 61 that year; (b) the Asset and Health Dynamics of the Oldest Old study, which included participants over age 70 and was merged with the HRS in 1998, and (c) two additional samples selected in 1998 to better represent the population of retired adults in the United States. Most HRS survey data are collected at 2-year intervals.

A subsample of HRS respondents consisting of women 80 years and older in 1998 formed the baseline for this study. Respondents were excluded if, in 1998, they reported a history of stroke or were unable to independently respond to survey materials (e.g., the CES-D, a measure of depressive symptoms). We then incorporated data from the six biennial waves (1998-2008).

Measures

Self-Reported Medical Conditions

Medical data (hypertension, diabetes, history of heart disease) and lifetime history of smoking were collected by self-report. Hypercholesterolemia was not included, because it was not reported in the data at every wave. Vital status was identified at each wave. In the case of deaths, the exact date within the 2-year period was not known.

Depressive Symptoms

Depression was measured using a shortened, 8-item form of the original Center for Epidemiological Studies Depression Scale (CESD; Radloff, 1977). Six of the eight items are

negatively worded and two are positively worded. Participants are asked to respond “yes” or “no” to each item (“was depressed,” “everything was an effort,” “sleep was restless,” “was happy,” “felt lonely,” “enjoyed life,” “felt sad,” “could not get going”), based on whether or not they had experienced it during the preceding week. Scores ranged from 0 to 8, with higher scores indicating greater depressive symptoms. Using HRS data, the reliability of the 8-item CES-D was adequate, with high Cronbach’s alpha (.81-.83; (Steffick, 2000). The 8-item CES-D has high internal consistency ($\alpha = .77$) and validity (Steffick, 2000) and is broadly used in epidemiological studies of late-life depression (Beekman et al., 1997). Recommended clinical cutoffs for this measure suggest interpreting CES-D scores ≥ 3 (Steffick, 2000) as indicative of probable clinical depression.

Vascular Depression Symptoms

In keeping with past work (Paulson & Lichtenberg, 2011) depression symptomatology and CVB were integrated to form a single variable representing vascular depression symptomatology. As displayed in Figure 5.1, respondents with 0 or 1 cerebrovascular risk factor (CVRF) and a CES-D score of 0 or 1 were assigned a score of 1 (description: very healthy). Those with 1 CVRF and CES-D scores of 1 or 2 were assigned a score of 2 (description: healthy), as were those with 0 CVRFs and a CES-D score of 2. Respondents with 2 or more CVRFs or a CES-D score ≥ 3 were assigned a score of 3 (description: high CVB or probable depression). Respondents with 2 or more CVRFs and CES-D scores of 3 or 4 were assigned a score of 4 (description: mild vascular depression symptoms). Those with more than 2 CVRFs and CES-D scores ≥ 5 were assigned a score of 5 on the vascular depression variable (description: moderate to severe vascular depression symptoms).

Self-Rated Health

Self-rated health was measured by comparing self-rated health reports (1=excellent, 2=very good, 3=good, 4=fair, 5=poor) at adjacent time periods. Positive values indicate health deterioration over a 2-year period. Negative values suggest improved health.

Functional Independence

Activities of daily living (ADLs) were measured using five criteria: bathing, eating, dressing, walking across a room, and getting in or out of bed. Instrumental activities of daily living (IADLs) were measured using three criteria: using a telephone, taking medication, and handling money. Scores on both indices indicate the number of items the respondent reported experiencing difficulty completing independently. Higher scores indicate greater disability.

Frailty

We measured frailty symptomatology based on Fried's (2001) conceptualization. Due to differences between the HRS data and Fried's model of frailty, we adapted the frailty index to include five symptoms: wasting, weakness, slowness, fatigue or exhaustion, and falls. The wasting criterion was met if a respondent reported loss of at least 10% of body weight over a 2-year period. The weakness criterion was met if she endorsed the question, "Because of health problems, do you have any difficulty with lifting or carrying weights over 10 pounds, like a heavy bag of groceries?" The slowness criterion was met if respondents answered in the affirmative to the question, "Because of a health problem, do you have any difficulty with getting up from a chair after sitting for long periods?" The fatigue or exhaustion criterion was met if the respondent answered in the affirmative to the question, "Since we last talked with you in [the last wave], have you had any of the following persistent or troublesome problems: . . . severe fatigue or exhaustion?" The falls criterion was met if the respondent answered in the

affirmative to the question, “Have you fallen down in the past 2 years?” While Fried’s criteria include low energy expenditure, this variable was not available in the HRS data. Instead, the frailty symptom list was modified to include falls, which was found to be an indirect measure of energy expenditure (Montero-Odasso et al., 2011). None of the frailty items was drawn from the CES-D. This frailty index was used as a semicontinuous variable. Complete frailty data were available at the 2000, 2004 and 2008 waves.

Statistical Methodology

Our primary objective was to test the described theoretical model, specifically addressing the hypothesis that vascular depression symptoms are an early indicator of a broader pattern of decline, and predict mortality indirectly through frailty. We tested a model temporal change that use the intercept-and-slope model (Raudenbush & Bryk, 2002; Raykov & Marcoulides, 2008). Mortality risk was modeled using a discrete time-survival term (Singer & Willett, 1993). Vascular depression and frailty were modeled using intercept and slope terms for each variable. Vascular depression intercept and slope latent variables predicted frailty intercept and slope variables, and both intercept and both slope terms were used to predict mortality. All five terms were regressed on self-rated health change, ADLs, IADLs, and age, thereby controlling for the influence of variables.

Longitudinal research with older adults is complicated by high attrition rates, in this case reflecting the high rates of mortality and disability. The conventional strategy of excluding respondents with incomplete data systematically underestimates disease severity and incorrectly estimates relationships with outcome variables. The full information maximum likelihood strategy (FIML; Arbuckle, 1996), was used to account for missing data. Specifically, auxiliary

variables identified as highly predictive of missing data (self-rated health change, ADLs, IADLs, and age) were used in both models to improve estimation of missing values (Graham, 2003). In this way, data from all 1,361 respondents with baseline data in the available sample were used, regardless of the availability of complete data on vascular depression and frailty symptoms. Data were prepared in SPSS V19 and analyses conducted using *Mplus*.

Results

The final sample included 1,361 respondents with a mean age of 84.12 years ($SD=4.10$) and 10.85 years of education ($SD=3.52$; Table 5.1). The sample was predominantly White. Attrition was primarily a function of mortality: Of the original 1998 sample, 13.2% had died by 2000, 30.7% by 2002, 44.6% by 2004, 57.8% by 2006, and 69.7% by 2008. Frailty rates were higher among respondents with higher vascular depression scores at baseline (Table 5.2).

The discrete-time survival analysis model (Figure 2) also had good overall fit ($RMSEA=.05$; $CFI=.97$; $X^2=234.84$, $p<.001$). In this model, high vascular depression symptom intercept scores significantly predicted attenuated increase in vascular depression scores over the course of the study and higher frailty symptom intercept scores. Control variables were omitted from Figure 2 for reasons of visual clarity, but are reported in Table 5.3. Higher scores on the vascular depression symptom intercept term were significantly predicted by greater ADL disability ($\beta=.47$, $p<.001$) and greater IADL disability ($\beta=.30$, $p<.005$). The vascular depression symptom slope term was not predicted by any of the control variables. Higher scores on the frailty symptom intercept term were significantly predicted by greater age ($\beta=.23$, $p<.001$) and greater ADL disability ($\beta=.32$, $p<.001$). The frailty symptom slope variable was also not predicted by any control variables, though there was a strong trend for older respondents to experience greater increase in frailty scores over the course of the study ($\beta=.10$, $p=.06$). Higher

scores on the mortality term, indicating greater mortality risk, were significantly predicted by greater age ($\beta=.21, p<.001$), more ADL disability ($\beta=.10, p<.001$), and greater IADL disability ($\beta=.20, p<.001$).

As shown in Figure 5.2, higher vascular depression intercept term scores significantly predicted lower vascular depression slope ($\beta=-.35, p=.03$), indicating that respondents with few vascular depression symptoms at baseline had a greater increase in these symptoms over the course of the study. Higher vascular depression intercept values predicted higher frailty intercept scores ($\beta=.26, p<.001$), indicating that respondents with more vascular depression symptoms at baseline (1998) had more frailty symptoms at the subsequent wave (2000). Similarly, higher vascular depression symptom slope predicted higher frailty symptom slope ($\beta= .10, p=.02$), indicating that increasing vascular depression symptoms predicted increasing frailty symptoms. Respondents with higher frailty scores had attenuated frailty symptom slopes over the course of the study ($\beta=-.33, p<.001$). The frailty symptom intercept score significantly predicted mortality ($\beta=.02, p=.04$), indicating that more frail respondents had higher mortality rates. The relationship between the vascular depression symptom intercept and mortality showed a trend toward significance ($\beta=.01; p=.09$). The indirect relationship between the vascular depression intercept term and mortality through the frailty intercept term was statistically significant ($\beta=.01, p=.04$).

Conclusions

Our primary finding is the elucidation of a pathway from vascular depression symptoms to frailty symptoms to death. In our sample of stroke-free women over the age of 80, vascular depression symptoms predicted mortality through frailty symptoms. These results support the

proposed theoretical framework by describing a late-life clinical trajectory characterized by high vascular depression and frailty symptoms. It is important to note that neither high CVB alone nor high depression symptoms alone were as good at predicting frailty and/or mortality. Support was found for the hypothesis that vascular depression symptoms are prodrome of frailty symptoms toward the end of life in older old women. We also found higher rates of vascular depression symptoms among elders with higher levels of ADL and IADL disability. In our sample of women over age 80, frailty symptoms were more common with high ADL disability. Mortality risk was significantly predicted by age and more ADL and IADL disability. Apart from the control variables; age, ADL and IADL disability, and self-reported health change, we found a progression from vascular depression symptoms to frailty symptoms to earlier mortality. These results support vascular depression theory (Alexopoulos et al., 1997b) and extend it by describing the emergence of vascular depression symptoms as an early stage in this chain of health decline. These findings also support work that relates frailty symptoms to mortality (Fried et al., 2001).

One of the biggest questions is whether the emergence of vascular depression symptoms are an early or late warning sign of decline. Will interventions at the point of discovering vascular depression symptoms avert or delay the onset of frailty and earlier mortality? Our results suggest that clinical interventions should be examined. Most significantly, the role of CVB emphasizes the importance of managing vascular risk throughout the lifespan so as to lessen its impact in late life. Arguably, the best intervention for the end-of-life trajectory described by these results is positive health behaviors across the lifespan. Obesity and resulting disorders such as diabetes and metabolic syndrome, for instance, are increasingly prevalent in the U.S. population (discussed in Bean, Stewart, & Olbrisch, 2008). High CVB slowly degrades

adaptive resources over many years. Early intervention may reduce rates of disability, preserve psychological health in late life, and delay the onset of frailty, thereby improving quality of life for older individuals.

The second course of investigation suggested by these results relates to slowing the transition to frailty, thereby preserving capacity for self-care and quality of life. Arean and colleagues (2010) have extensively researched behavioral interventions for “depression-dysexecutive syndrome,” which is generally analogous to vascular depression. Their results suggest that this skills-based intervention can improve capacity for self-care and reduce symptoms of depression. This intervention’s effect on the transition to frailty has not been explicitly studied.

Our findings’ primary limitation is the use of self-reported medical data. Future research using the HRS data could make use of biomarkers newly available in the 2008 and 2010 data releases. This would also facilitate use of, for instance, blood pressure or glucose response as continuous variables that predict development of depression symptoms and frailty. Our results also describe a depression subtype with a clinical course that differs significantly from traditional major depressive disorder. Given the unusually late onset of vascular depression, its relationship to medical comorbidities, and other unique characteristics of this depression subtype, consideration of a vascular depression specifier for the DSM-IV-TR Major Depressive Disorder diagnosis is indicated.

APPENDIX A

Table 2.1

Demographic, independent and dependent statistics for 1,355 participants at baseline (1998)

	Mean (SD)
Age	84.8 (4.1)
Years of Education	10.86 (3.52)
Ethnic Distribution	
White	79.5%
Black	14.3%
Hispanic	5.2%
Other	1%
CVB (total count 0-4)	1.31 (.92)
TICS	18.14 (6.16)
CES-D	2.12 (2.00)

Abbreviations: CVB = Cerebrovascular Burden; TICS = Telephone Interview for Cognitive

Status; CES-D = Center for Epidemiological Studies Depression Scale

Table 2.2

Parameter estimates, standard errors, t-values, and p-values associated with the conditional LGC model (see Equations (2)).

Predictor	Estimate	SE	t-Value	p-Value
Regression of Initial Depression on				
Age	0.023	0.013	1.775	0.076
CVB	0.193	0.361	0.534	0.461
CF	-0.083	0.113	-0.738	0.593
Education	-0.155	0.045	-3.467	0.001
CVB*Education	0.027	0.031	0.868	0.385
Regression of Rate of Change in Depression on				
Age	-0.009	0.007	-1.278	0.201
CVB	0.256	0.206	1.241	0.215
CF	-0.042	0.058	-0.729	0.466
Education	0.039	0.024	1.613	0.107
CVB*Education	-0.014	0.017	-0.823	0.410

CF = cognitive functioning, CVB*Education= interaction of cerebrovascular burden and cognitive functioning.

Table 2.3

Parameter estimates, standard errors, t-values, and associated p-values associated with the parsimonious conditional LGC model (no interaction term; see note to Table 1 for used variable names.

Predictor	Estimate	SE	t-Value	p-Value
Regression of Initial Depression on				
Age	0.023	0.013	1.730	0.084
CVB	0.481	0.107	4.513	<0.001
CF	-0.085	0.113	-0.751	0.453
Education	-0.118	0.016	-7.230	<0.001
Regression of Rate of Change in Depression on				
Age	-0.009	0.007	-1.278	0.201
CVB	0.097	0.055	1.787	0.074
CF	-0.042	0.058	-0.733	0.464
Education	0.019	0.009	2.217	0.027

CF = cognitive functioning.

Table 2.4

Percentages of participants with high and low CVB and education with probable depression

based on CESD score cutoffs of 3 and 5

		Wave			
		1998	2000	2002	2004
		N=1,355	N=990	N=737	N=547
CES-D Cutoff of 3					
CVB	Low	31.3	27.7	28.6	28.1
	High	42	41.6	40.4	45.1
	X ²	16.04***	20.33***	10.48***	15.38***
Years of Educ	0-12	40	35.8	36.1	36.3
	12+	23.3	25.5	25.1	25.5
	X ²	18.38***	9.64**	8.40**	5.86**
CES-D Cutoff of 5					
CVB	Low	12.2	10.8	10.2	8.8
	High	18.6	19.3	20.4	22
	X ²	10.49**	13.99***	14.70***	18.09***
Years of Educ	0-12	16.6	16.4	16.4	13.8
	12+	9.5	8.3	7.8	11.1
	X ²	10.68***	12.97***	9.67**	0.697

Table 3.1

Sample Description at the 2000 wave (baseline).

Variable	Mean	SD
Age	85.63	3.82
Education	11.03	3.42
CVB	1.03	0.82
CESD	2.07	1.98
TICS	18.13	5.86
BMI	24.40	4.86
Self-Rated Health Change	3.36	0.83
Ethnic Distribution	Percentage	
White	79.7%	
Black	14.2%	
Hispanic	5.2%	
Other	1.1%	
% High CVB	42.2%	

Note. CVB=Number of symptoms comprising cerebrovascular burden (heart disease, diabetes,

hypertension scored 0-3). CESD=Center for Epidemiological Studies Depression Scale,

TICS=Telephone Interview for Cognitive Status, BMI=Body Mass Index

Table 3.2

Results of logistic regressions predicting incidence of mortality between 2000 and 2006 and between 2000 and 2008.

Variable	Predicting death between 2000 and 2006				Predicting death between 2000 and 2008			
	B	SE	Wald	Exp(B) 95% CI	B	SE	Wald	Exp(B) 95% CI
Age	0.15	0.02	55.65 ^ψ	1.12-1.21	0.15	0.02	46.86 ^ψ	1.11-1.22
Education	-0.03	0.02	1.61	.93-1.02	-0.03	0.02	1.54	.93-1.02
BMI	-0.07	0.02	17.27 ^ψ	.91-.97	-0.07	0.02	18.76 ^ψ	.90-.96
CVB	0.46	0.09	26.74 ^ψ	1.33-1.88	0.56	0.09	36.19 ^ψ	1.46-2.10
Self-Rated Health	0.17	0.09	3.21 [§]	.98-1.42	0.15	0.10	2.37	.96-1.41
2000 CESD Score	0.08	0.04	4.26*	1.00-1.16	0.07	0.04	3.46 [§]	.99-1.16
'98-'00 TICS Drop	0.35	0.21	2.81 [§]	.94-2.12	0.05	0.22	0.06	.69-1.62
Constant	-12.00	1.82	43.44		-11.31	1.97	32.87	

Note. BMI=Body Mass Index. CVB=Cerebrovascular Burden, SR Health Change=Change in Self-Rated Health from previous wave, CESD=Center for Epidemiological Studies Depression Scale, TICS=Telephone Interview for Cognitive Status. TICS Drop reflects incidence of decline on TICS score greater than 6 points between 1998 and 2000.

[§]p between .05 and .10, *p<.05. ^ψ p<.001. df=1 for all comparisons.

Table 3.3

Results of logistic regression analyses predicting death at 2002, 2004, 2006 and 2008 waves based on depressive symptoms and incidence of cognitive decline.

Predicting Death in 2002					Predicting Death in 2004				
	B	SE	Wald	Exp(B) 95% CI		B	SE	Wald	Exp(B) 95% CI
2000 CVB	.54	.11	26.83 ^ψ	1.40- 2.11	2002 CVB	.43	.12	11.97 ^ψ	1.21- 1.97
2000 CESD	.08	.04	3.90*	1.00- 1.18	2002 CESD	.17	.05	13.71 ^ψ	1.09- 1.31
'98-'00 TICS >1SD	.40	.23	2.92 [§]	.94- 2.33	'00-'02 TICS >1SD	.76	.27	8.11 ⁺	1.27- 3.61
Constant	-2.49	.18	183.52 ^ψ		Constant	-2.68	.22	146.83 ^ψ	

Predicting Death in 2006					Predicting Death in 2008				
	B	SE	Wald	Exp(B) 95% CI		B	SE	Wald	Exp(B) 95% CI
2004 CVB	.22	.14	2.61	.95- 1.64	2006 CVB	.44	.17	6.93 ⁺	1.12- 2.16
2004 CESD	.03	.06	0.29	.92- 1.15	2006 CESD	.07	.07	1.09	0.94- 1.22
'02-'04 TICS >1SD	.39	.34	1.36	.77- 2.85	'04-'06 TICS >1SD	1.12	.43	6.86 ⁺	1.33- 7.06
Constant	-1.79	.22	64.51		Constant	-2.15	.30	50.13 ^ψ	

Note. CVB=Cerebrovascular Burden. CESD=Center for Epidemiological Studies Depression Scale. TICS=Telephone Interview for Cognitive Status. TICS Drop reflects incidence of decline on TICS score greater than 6 points between waves as indicated.

[§]p=.088, *p<.05, + p<.01, ^ψ p<.001. df=1 for all comparisons.

Table 4.1

Description of Sample

Variable	2000 (N=984)	2004 (N=459)
	Mean (SD)	Mean (SD)
Age	85.62 (3.82)	84.53 (3.03)
Education	11.02 (3.44)	11.24 (3.13)
ADLs	.64 (1.12)	0.24 (0.69)
IADLs	.21 (.55)	0.10 (0.38)
2000 CESD	2.07 (1.98)	1.55 (1.70)
	<u>% of Samp</u>	<u>% of Samp</u>
Ethnicity		
White	79.6	80.2
Black	14.3	12.4
Latina	5.3	6.1
Other	1	1.5
CV Risk Factors		
Hypertension	57.6	52.9
Diabetes	11.5	7
Cardiac	34.8	25.1
Smoking	34.9	34.9
Non-CV Health		
Arthritis	69.6	59.3
Pulmonary	7.2	4.8
Cancer	14.8	14.6
2000 CVB (% High)	42.2	33.3
2000 CESD (% High)	32.8	22

Table 4.2

Prevalence in 2000 and incidence in 2004 of frailty among respondents without high CVB or probable depression (CESD score ≥ 3), respondents with high CVB or probable depression, and respondents with both high CVB and probable depression .

	2000 Prevalence		2004 Incidence	
	n	% Frail	n	% Frail
Low CVB, Low CESD	413	20.1%	248	25.0%
High CVB or High CESD	404	34.9%	168	35.7%
High CVB, High CESD	86	51.5%	43	55.8%

Table 4.3

Results of logistic regression predicting frailty in 2000. N=984.

	Block 1				Block 2			
	B	S.E.	Wald	95% CI	B	S.E.	Wald	95% CI
Age	.06	.02	9.11**	1.02-1.11	.06	.02	9.52**	1.02-1.11
Education	.02	.02	0.97	.98-1.07	.03	.02	2.14	.99-1.08
ADLs	.64	.08	57.89***	1.61-2.24	.60	.09	49.61***	1.54-2.15
IADLs	-.02	.16	0.02	.72-1.33	-.03	.16	0.03	.71-1.33
Arthritis	1.09	.20	30.47***	2.03-4.40	1.05	.20	28.18***	1.94-4.23
Pulmonary	.41	.28	2.16	.87-2.62	.41	.28	2.08	.86-2.61
Cancer	.34	.21	2.62	.93-2.14	.33	.22	2.33	.91-2.12
S-R Hlth Δ	.46	.10	20.91***	1.30-1.93	.39	.10	14.58***	1.21-1.80
Vascular Dep.					.41	.11	13.26***	1.21-1.88
Constant	-9.26	1.84	25.25***		-9.53	1.85	26.68***	

p \leq 05; **p \leq 01; *p \leq 001; S-R Hlth Δ =Self-rated health change;ADLs=Activities of Daily*

Living; IADLs=Instrumental Activities of Daily Living; Vascular Depression – respondents with neither high CVB or CESD scores \geq 3 scored 0, respondents with high CVB or CESD scores \geq 3 scored 1, respondents with both high CVB and CESD scores \geq 3 scored 2.

Table 4.4

Results of logistic regression predicting frailty in 2004. N=459.

	Block 1				Block 2			
	B	S.E.	Wald	95% CI	B	S.E.	Wald	95% CI
Age	.05	.03	1.96	.98-1.12	.05	.03	2.03	.98-1.12
Education	-.03	.03	.75	.91-1.04	-.02	.03	.43	.91-1.05
ADLs	.50	8.00	7.85**	1.16-2.36	.49	.18	7.21**	1.14-2.32
IADLs	.45	.32	1.95	.83-2.93	.43	.32	1.85	.83-2.86
Arthritis	.38	.22	2.99	.95-2.25	.33	.22	2.14	.90-2.14
Pulmonary	-.74	.55	1.76	.16-1.42	-.57	.56	1.04	.19-1.69
Cancer	.23	.29	.63	.71-2.23	.19	.30	.42	.68-2.16
S-R Hlth Δ	.69	.17	15.89***	1.42-2.81	.65	.18	13.53***	1.35-2.70
Vascular Dep.					.49	.16	9.12**	1.19-2.24
Constant	-7.08	2.99	5.62*		-7.35	3.01	5.96*	

** $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; S-R Hlth Δ =Self-rated health change; ADLs=Activities of Daily*

Living; IADLs=Instrumental Activities of Daily Living; Vascular Depression – respondents with neither high CVB or CESD scores ≥ 3 scored 0, respondents with high CVB or CESD scores ≥ 3 scored 1, respondents with both high CVB and CESD scores ≥ 3 scored 2.

Table 5.1

Description of the sample at baseline (1998)

Variable	Mean (SD)
Age	84.12 (4.10)
Years of Education	10.85 (3.52)
CVB	1.31 (.92)
ADLs	.63 (1.16)
IADLs	.23 (.59)
Self-Rated Health Change	.23 (1.10)
	<u>% of Sample</u>
Ethnic Distribution	
White	79.7
Black	14.3
Hispanic	5.2
Other	0.8
Medical Diagnoses	
Hypertension	53.8
Diabetes	11.3
Cardiac Disease	30.9
Arthritis	64.8
Pulmonary	
Disease	7.2
Cancer	13.8

Table 5.2

Frequencies and mean (SD) frailty scores by Wave 4 VD score

Wave 4		Description	Mean (SD) Frailty Score		
VD Score	Freq.		Wave 5	Wave 7	Wave 9
1	303	Very Healthy	1.58 (1.34)	1.88 (1.27)	2.13 (1.26)
2	273	Healthy	1.18 (1.20)	2.06 (1.15)	2.48 (1.05)
3	562	High CVB or Probable Depression	2.05 (1.28)	2.31 (1.19)	2.52 (1.07)
4	121	Vascular Depression, Mild	2.52 (1.19)	2.60 (1.16)	1.77 (1.01)
5	96	Vascular Depression, Moderate-Severe	2.48 (1.30)	2.82 (1.14)	3.08 (1.31)

Table 5.3

Unstandardized regression coefficients for control variables (age, self-rated health change, ADLs and IADLs) on vascular depression intercept and slope, frailty intercept and slope, and mortality

Latent Var.	Control Var.	β	S.E
VD-Int.			
	Age	-0.04	0.05
	Self-Rated Health Δ	-0.10	0.05
	ADLs	0.47***	0.07
	IADLs	0.30**	0.11
VD-Slope			
	Age	0.01	0.12
	Self-Rated Health Δ	0.16	0.12
	ADLs	-0.02	0.14
	IADLs	0.46	0.37
Frailty-Int			
	Age	0.23***	0.04
	Self-Rated Health Δ	0.02	0.04
	ADLs	0.32***	0.06
	IADLs	-0.07	0.10
Frailty-Slope			
	Age	0.10	0.05
	Self-Rated Health Δ	-0.06	0.04
	ADLs	-0.06	0.08
	IADLs	0.17	0.17
Mortality			
	Age	0.21***	0.02
	Self-Rated Health Δ	0.00	0.02
	ADLs	0.10***	0.02
	IADLs	0.20***	0.04

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

APPENDIX B

Figure 1.1

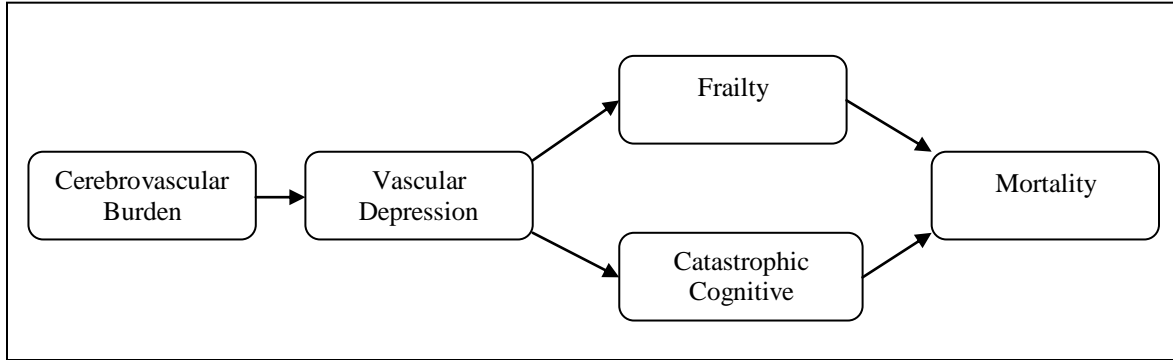
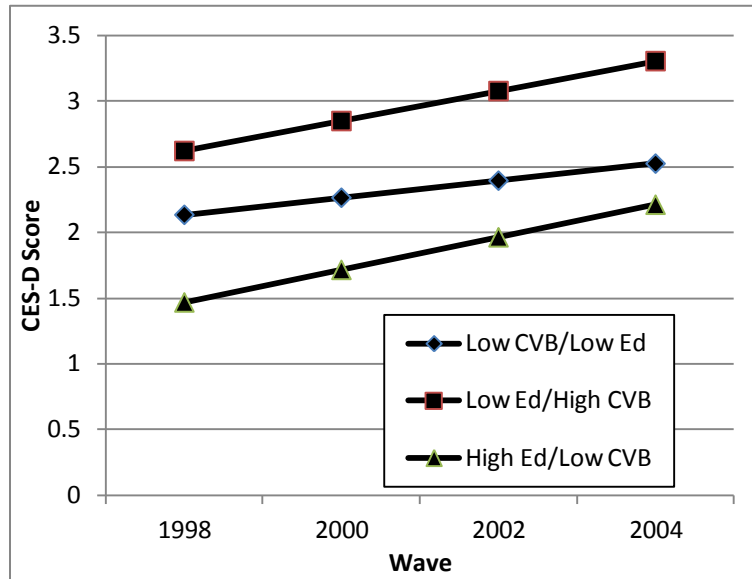
Conceptual model

Figure 2.1

Plotted growth curves depicting CES-D score over time for the low CVB/low education, low CVB/high education, and high education/low CVB groups.



Note: For reasons of visual presentation, the education variable was dichotomized for this figure (Low Ed: 12 years or less, High Ed: more than 12 years).

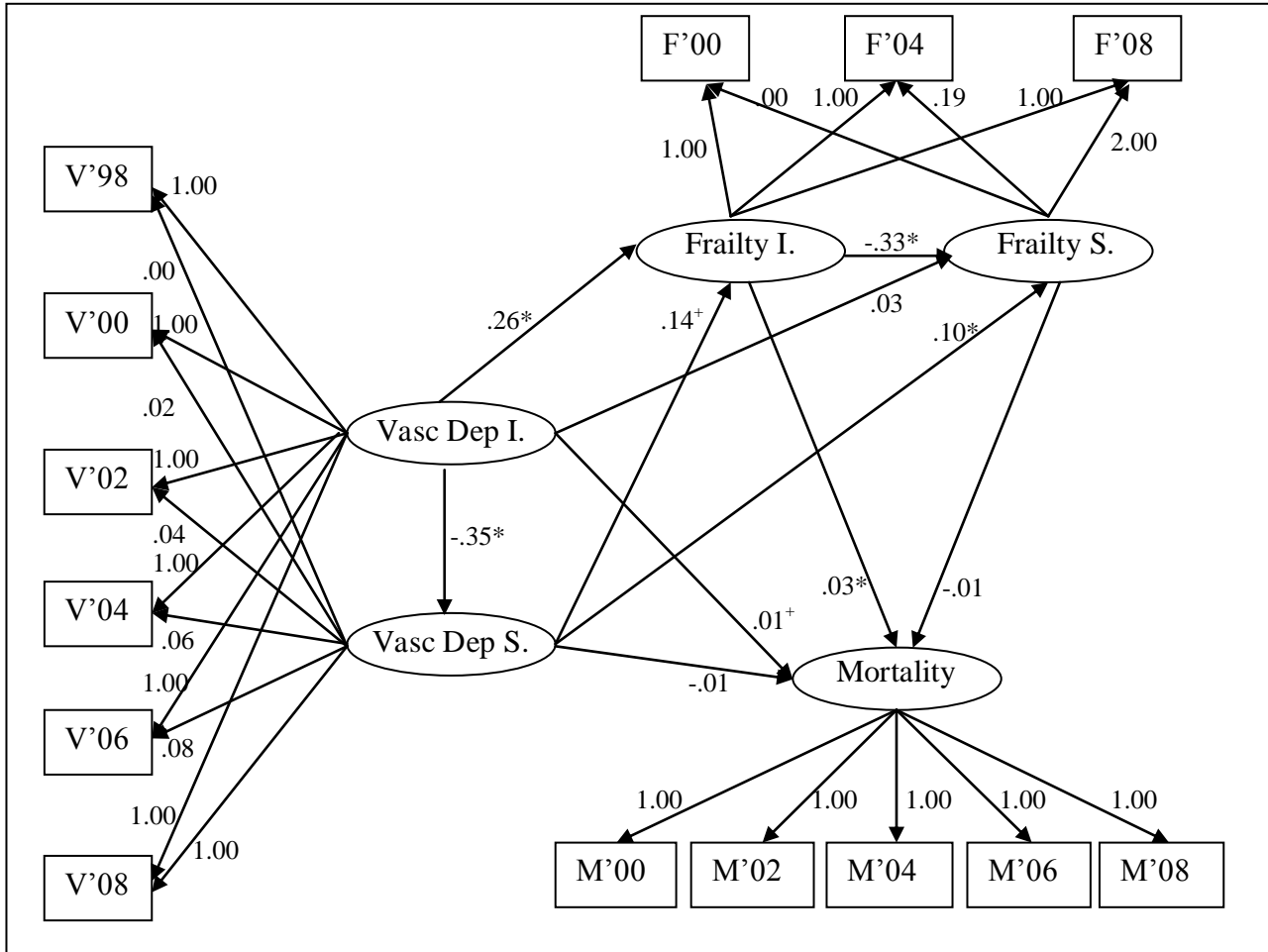
Figure 4.1

Specification of Vascular Depression variable based on CESD score and number of cerebrovascular risk factors reported at wave 4

CESD Score	Wave 4 CVB					Total
	0	1	2	3	4	
0	86	152	77	25	3	343
1	65	135	74	27	3	304
2	43	95	68	22	1	229
3	26	78	53	16	2	175
4	19	37	34	14	2	106
5	5	34	28	8	2	84
6	5	26	23	13	0	67
7	3	16	10	5	0	34
8	0	6	4	3	0	13
Total	262	576	371	133	13	1355

Figure 4.2

Structural model depicting slope and intercept terms for vascular depression symptoms and frailty symptoms, and a discrete-time survival term reflecting mortality risk predicted by all four factors.



⁺p<.10; *p<.05; V=Vascular Depression. F=Frailty. M=Mortality.

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ABSTRACT**VASCULAR DEPRESSION: AN EARLY INDICATOR OF DECLINE**

by

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August 2013

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Women over the age of 80 represent a rapidly growing demographic group. While older women live longer than men, they do so with more years of disability and frailty. The emergence of geriatric disorders such as vascular disease, depression, frailty and cognitive decline in the aging US population place additional strain and expense on the already overburdened public health care system. Meanwhile, integrated models of care are associated with preserved functional independence, reduced medical costs, and greater satisfaction for both health care providers and patients. Implementation of integrated care demands process-models of disease that contextualize symptoms within broader patterns of decline. This dissertation proposes a model representing a hypothesized late-life clinical trajectory following from high cerebrovascular burden. The hypothesized trajectory includes higher rates of depression (of vascular origin), cognitive decline, frailty and shortened remaining lifespan. Different facets of this model are tested in the four studies that comprise this dissertation.

The sample was drawn from the Health and Retirement Study; a longitudinal, demographically-representative data sample of older adults in the United States. The sub-sample

used in this dissertation included 1,368 stroke-free women over the age of 80 at baseline (1998). This sub-sample was followed for 10 years.

The first study tested the hypotheses that high CVB predicts greater depression symptoms, and that brain reserve (i.e.: education) protects elders from developing depression symptoms. A latent growth curve was used to identify differences in depression at baseline and over time based on CVB, cognitive functioning, education and age. Results indicate that at any level of CVB, older women with more education experienced fewer depression symptoms. Results support brain reserve theory and the vascular depression hypothesis. These results suggest that having greater education may postpone development of clinically-significant depressive symptoms resulting from high CVB, thereby preserving mood in late life.

The second study tested the hypothesis that variables representing the three domains of Rowe and Kahn's Healthy Aging framework predict longevity in this sample of stroke-free women over the age of 80. The "avoidance of disease" domain was characterized in this paper as CVB - chronic comorbidities that slowly erode adaptive functioning over many years. The "sustained engagement" criteria was conceptualized as depression, and deficits in the "preservation of cognitive and physical functioning" domain were identified as rapid cognitive decline. We found that at most waves (2002, 2004, 2006) mortality was predicted by CVB, depressive symptoms and cognitive drop measured 2 years prior. CVB and depressive symptoms at the 2000 wave predicted mortality at 6 and 8-years. Older women with the greatest longevity had low CVB, robust cognitive functioning and few depression symptoms, supporting successful aging theory and terminal cognitive drop.

The third study tested the hypothesis that vascular depression is a prodrome for frailty. At baseline, the prevalence of frailty was 31.5%. Over a 4-years the incidence of frailty was

31.8%. After controlling for age, education, ADL and IADL functioning, arthritis, pulmonary disorders, cancer, and self-rated health, vascular depression significantly predicted new cases of frailty. These findings suggest that vascular depression is a prodrome for frailty.

The fourth study tested the proposed model using structural modeling. The model demonstrated good overall fit and a significant indirect pathway from vascular depression to mortality through frailty was identified. Results support the proposed theoretical framework and suggest that vascular depression symptoms are associated with a clinical trajectory including more frailty symptoms and shorted remaining lifespan. This finding supports integrated care for geriatric patients and suggests specific targets for intervention with older patients experiencing vascular depression symptoms.

AUTOBIOGRAPHICAL STATEMENT

DANIEL PAULSON

Daniel Paulson is a native of Keyser, West Virginia, a small Appalachian town in the eastern panhandle of West Virginia. He completed his Bachelor's degree in Psychology at Virginia Tech in 2002. He then earned a Master's degree in Psychological Sciences at James Madison University where he studied depression with his advisor, Dr. Gregg Henriques. In 2006 he began the Clinical Psychology program at Wayne State University where he works with Dr. Peter Lichtenberg. His primary area of research addresses the relationships between cerebrovascular disease and disorders of late life such as vascular depression, cognitive decline and frailty. Daniel is presently a doctoral candidate and hopes to complete an APA-accredited pre-doctoral internship in 2013. Upon completion of his PhD, he intends to complete a post-doctoral internship in geriatric neuropsychology and obtain a research-intensive academic faculty position.