Association of vascular function and cognitive impairment no dementia (CIND)

by

Anna Braslavsky
B.Sc., University of Alberta, 2009

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Supervisory Committee

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Abstract

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Cognitive impairment no dementia (CIND) is conceptualized as a stage of cognitive decline between normal aging and onset of dementia. As persons with CIND are at high risk of developing dementia, efforts to determine early predictors of cognitive decline are warranted to advance both clinical knowledge and practice. Recent evidence suggests persons with CIND may have changes in vascular function compared to non-impaired peers, which may have clinical potential to differentiate those with and without CIND. The purpose of this study is to determine whether vascular functioning, examined both by individual indicators and as an aggregate vascular factor, will be associated with cognitive impairment. It is expected that the individual vascular indicators of hypertension, diabetes, stroke, and heart problems will be related to cognitive status classification, with poorer vascular function being more strongly associated with CIND as compared to the control group. Further, it is expected that examining the aggregate vascular factor in a multivariate approach will be more strongly associated with cognitive status than examining the vascular indicators individually. Data for this study were collected in the Victoria Longitudinal Study (VLS), a large-scale longitudinal, sequential study of community-dwelling older adults in Victoria, British Columbia. Cognitive group status was determined by a distributional approach based on scores on 5 cognitive

reference measures. The associations between all vascular factors and cognitive status groups were assessed using chi-square analyses. Univariate analyses were then carried out using ordinal logistic analysis. A multivariate approach using discriminant analysis was then used to determine if cognitive status group membership was associated with vascular function based on linear combinations of vascular indicators. Contrary to expected results, we did not find a significant association between any of the vascular indicators (i.e., blood pressure classification, severity of stroke, severity of heart troubles, and severity of diabetes) and the cognitive status classifications. Further, group membership was not associated with any of the individual vascular markers, or by a multivariate combination of the indicators. Several reasons for this study's findings include discrepant definitions of cognitive impairment in the literature, sample characteristics (i.e. high education, low base rate of vascular problems), and methodological considerations. Future research objectives should address the longitudinal association of vascular function and cognitive status.

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Acknowledgments

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Introduction

Mild cognitive impairment (MCI) has been conceptualized as a stage of cognitive decline between normal healthy aging and onset of dementia, primarily exhibited by deficits in memory (Tuokko & McDowell, 2006). However, there is controversy regarding the nature and criteria required for a classification of MCI with many proposed classification schemes. Despite the lack of consensus on the definition and diagnostic validity of MCI, a period of cognitive decline preceding onset of dementia has been widely accepted and has received great attention as a potential period of intervention in the early treatment of dementia (DeCarli, 2003; Morris et al., 2001a; Petersen et al., 1999).

As persons with MCI appear to be at high risk of developing dementia, current efforts to determine the early predictors of cognitive decline are warranted to advance both clinical knowledge and practice. Recent evidence suggests that persons with MCI may have changes in vascular function compared to persons undergoing normal, healthy aging, and that these changes may have clinical potential to distinguish those with MCI from those who are not cognitively impaired (Artero et al., 2008; Kivipelto et al., 2001). Furthermore, it is possible that changes in vascular function could be used as predictors of cognitive decline. These physiological markers of cognitive decline may have a significant clinical utility, as they are simple and non-invasive measures of biofunction that could be used in conjunction with other measures in developing screening tools for early intervention.

Definitions of Cognitive Impairment

The concept of MCI has been largely debated, with many differing viewpoints on its validity as a midway stage between normal aging and dementia. This controversy is largely due to inconsistent findings regarding its etiology, stability of classification, and progression over time. A prominent research group led by Petersen and colleagues (1999) have suggested a definition of MCI as: 1) memory impairment beyond what is predicted for a person's age and intellectual abilities, 2) relatively intact functioning in other cognitive domains, and 3) no functional decline as seen in dementia. Longitudinal evaluation of cognitive abilities in persons with MCI has revealed strong deficits in tasks of episodic memory both at baseline and over time in persons who convert to a diagnosis of AD over a four-year period (Albert, Blacker, Moss, Tanzi, & McArdle, 2007). This is suggested to be related to atrophy evident in the medial temporal lobe, specifically the entorhinal cortex and hippocampus (Atiya, Hyman, Albert, & Killiany, 2003).

Others have argued that this definition is too restrictive, suggesting that MCI represents a more heterogeneous group of individuals who may exhibit deficits in cognitive domains other than memory (Backman, Jones, Berger, Laukka, & Smith, 2005). In a meta-analysis of forty-seven studies, Backman et al. (2005) examined the extent of impairment in various cognitive domains, including attention, episodic memory, executive functioning, perceptual speed, verbal ability, and visuospatial ability in persons with preclinical Alzheimer's disease. The authors concluded that cognitive impairment in MCI is quite widespread and global, with the largest and most replicable deficits in the domains of episodic memory ($d = 1.03$), executive functioning ($d = 1.07$) , and perceptual speed ($d = 1.11$). A smaller, but still significant, deficit was reported in the domains of

verbal ability (d = 0.79), visuospatial skill (d = 0.64), and attention (d = 0.62). Further, large deficits were found on a measure of global cognitive ability (d = 1.19). Based on such findings, a more broad set of inclusion criteria have been proposed for a preclinical period of impairment in memory and/or other cognitive domains – termed cognitive impairment, no dementia (CIND; Graham et al., 1997; Tuokko et al., 2003). Within this framework, classification as cognitively impaired is based on deficits in one or more cognitive domains, which may or may not include memory impairment. Commonly used criteria for CIND are based on those employed by the Canadian Study of Health and Aging (CSHA; Graham et al., 1997) in which persons were classified as CIND based on exclusion of dementia and clinical judgment of some form of cognitive impairment. This more encompassing definition allows for the inclusion of persons exhibiting changes in cognition in other domains known to be affected in the neurodegenerative processes associated with dementia. The current study will employ the more broad and inclusive CIND classification; however, as a multitude of terminology abounds in the literature, we will also make reference to previous work using the MCI classification.

There remains a great deal of interindividual differences among persons with MCI, particularly among those with deficits only in the domain of episodic memory and those with additional cognitive deficits. Several subtypes of MCI have been suggested, most commonly based on Petersen's (2004) criteria. Based on these criteria, persons with deficits in memory functioning in the context of normal functioning in other cognitive domains are classified as being amnestic-MCI (a-MCI). Others have defined a-MCI more stringently, as impairment (1.5 standard deviations below gender- and age-matched mean performance) on two or more tests of memory function, while performance on tests of

other cognitive variables is within normal range (Loewenstein et al., 2009). Further, persons with deficits in episodic memory plus at least one other nonmemory domain have been labeled as multiple-domain MCI (md-MCI), which is theoretically postulated as representing a deeper and more global form of cognitive impairment with a more widespread neuropathology (Palmer, Backman, Small, & Fratiglioni, 2006; Petersen, 2004). A similar approach can be applied to the more inclusive CIND classification to specify whether the cognitive impairment is limited to a single domain or whether it is more pervasive. An impairment in a single cognitive domain, which may or may not be memory, is indicated as single-domain CIND (sd-MCI) while deficits in two or more cognitive domains is defined as multiple-domain CIND (md-CIND).

Longitudinal follow-up of persons with different MCI subtypes illuminates some of the confounds posed by lack of consensus on a definition, namely that cognitive impairment at 2- or 3-year follow-up differed as a function of subtypes (Loewenstein et al., 2009; Palmer et al., 2006). Palmer and colleagues (2006) investigated the risk of progressing to a diagnosis of AD in older adults enrolled in the Kungsholmen Project based on the different subtypes of MCI. After a three-year follow-up, 33% of those individuals classified as a-MCI converted to a diagnosis of AD, with a relative risk of 9.5 compared to controls. However, those with sd-MCI did not have an increased risk of developing AD as compared to those who were cognitively intact at the initial time of testing. Further, 75% of those with md-MCI progressed to AD over the follow-up period, with a relative risk of 25.3 compared to initially intact participants. This finding was replicated by Matthews and colleagues (2008), lending support to the notion that the md-

MCI group may have greater impairment than other subtypes of MCI, likely due to multiple brain areas and processes affected in the preclinical phase of AD.

A similar issue was examined by DiCarlo and colleagues (2007) in longitudinal evaluation of progression to dementia based on different subtypes of CIND as defined in the CSHA (Graham et al., 1997). Over approximately four years, 9.8% of participants with sd-CIND (memory domain), 15.8% of participants with sd-CIND (nonmemory domain), and 19.0% of participants with md-CIND converted to dementia. These results indicate that conversion to dementia may be more highly associated with impairments in nonmemory domains, and this association becomes more pronounced when several cognitive domains are affected. This suggests that a narrow focus on the amnestic type of cognitive impairment may in fact be too restrictive and not capture those individuals more likely to progress to dementia over time.

Vascular Factors and CIND

Several biomarkers have been found to be associated with cognitive decline seen in MCI, including microtubule-associated proteins tau (t-tau), phosphorylated tau (p-tau) and levels of amyloid ($A\beta_{42}$) in cerebrospinal fluid (Fjell et al., 2010; Mariani, Monastero, & Mecocci, 2007). Levels of these cerebrospinal fluid (CSF) biomarkers were found to be related to brain atrophy in several regions, including lateral posterior, inferior parietal, lateral temporal, entorhinal cortices, and mesial and lateral temporal, suggesting that they may have utility in predicting cognitive decline (Fjell et al., 2007). However, while research examining the use of these biomarkers is important and needed, there are limitations to the use of CSF biomarkers in clinical practice. Collection of samples of CSF is costly, invasive, and time-consuming, and is currently not easily

available to all elderly persons within the healthcare system. It is therefore necessary to examine the utility of biomarkers that are noninvasive, easy to measure, and inexpensive, while recognizing that these markers may be more removed from the mechanisms underlying cognitive decline. Ideally, these biomarkers would include physiological measures routinely assessed by a family physician and could be used in the development of screening tools for early intervention. Findings from recent research investigating the association between physiological markers and cognitive impairment suggest that measures of vascular function may be among the most promising in the search for early noninvasive markers of decline.

Several vascular factors have been postulated as being associated with increased risk of developing cognitive impairment over time, including hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), and high fasting glucose level, which together are signs of metabolic syndrome (Yaffe, Weston, Blackwell, & Krueger, 2009). In a prospective study examining the risk of developing cognitive impairment in women with metabolic syndrome, Yaffe and colleagues (2009) found an increased risk of developing cognitive impairment over a period of four years associated with metabolic syndrome. Further, there was a 23% increase in risk of developing cognitive impairment for every additional metabolic syndrome component, suggesting that the individual components of the metabolic syndrome may be associated with risk of cognitive impairment. Metabolic syndrome is also associated with increased risk of stroke, type II diabetes and cardiovascular disease, evidenced in the study by a trend of women with metabolic syndrome being more likely to have a history of myocardial infarction. These findings suggest that research evaluating the role of vascular risk factors in the

progression of cognitive impairment should examine the changes in vascular function at the level of both the individual components of the syndrome and its potential outcomes (i.e. stroke, heart problems, and diabetes), as well as a larger systemic factor.

Blood Pressure

Among the research investigating the links between vascular function and MCI, one of the most commonly studied factors has been blood pressure, more specifically hypertension. Hypertension has been implicated in the etiology of dementia, and it has been suggested that hypertension is also a risk factor for conversion from normal, healthy aging to MCI (Lopez et al., 2003; Tervo et al., 2004). Further, hypertension is associated with conversion from MCI to the deeper, more global cognitive impairments seen in dementia (Artero et al., 2008). In a study following a population-based sample of community-dwelling older adults for four years, Artero and colleagues (2008) examined a wide range of biological, physiological and lifestyle risk factors for MCI and dementia. The authors used a classification scheme in which persons scoring in the lowest quartile on at least one cognitive test (memory or nonmemory domain) compared to age- and education-matched comparison group were categorized as MCI. They concluded that persons with MCI could be distinguished from healthy controls on the basis of several factors, including hypertension, history of diabetes, cardiovascular antecedents such as history of myocardial infarction, coronary surgery, coronary angioplasty or arterial surgery of the legs for arteritis, and stroke. Moreover, persons with these risk factors were more likely to convert to dementia over the four-year follow-up period, suggesting that these cardiovascular risk factors may be implicated in the downward trajectory of cognitive status in persons developing dementia. While much attention has been paid to

clinical cutoffs for hypertension, it has also been suggested that elevated systolic and diastolic blood pressure not reaching clinical levels for hypertension may also contribute to risk of MCI. DeCarli and colleages (2001) found that elevated diastolic blood pressure in midlife (age 42-56) was associated with development of amnestic MCI later in life in persons without a history of symptomatic cerebrovascular disease, suggesting that even relatively small elevations in blood pressure may contribute to risk of developing cognitive impairment.

While these results are promising, not all studies in this area have yielded positive results for the relationship between hypertension and MCI. Johnson et al. (2008) did not find a significant association between baseline hypertension and cognitive performance at baseline, nor was it associated with incident MCI once potential confounds (i.e., age, race, blood pressure control) were included in the analyses. The authors suggest that the inclusion of these potential confounds could strongly impact results obtained by other groups and could perhaps attenuate relationships seen in the literature. However, Johnson and colleagues report data from the Women's Health Initiative Memory Study and it has been suggested that the relationship between vascular factors and MCI may be stronger in men than in women (Artero et al., 2008), though further studies are needed to replicate this finding.

Additionally, it has been suggested that some of the mixed findings within this literature may stem from the different definitions and classification schemes used to categorize persons as MCI. Many studies on this topic have examined persons with MCI as a homogeneous group, which is in conflict with the commonly held view that MCI represents a clinical entity with many possible presentations (e.g., deficits in memory,

executive functioning). Due to the broad nature of this concept, it is possible that different subtypes of MCI will show different cognitive and physiological trajectories over time, which may obfuscate findings in studies treating MCI as a homogeneous entity. Further complicating this issue, those with cognitive impairment in a single cognitive domain (memory or nonmemory) may have very different etiological and prognostic considerations than those who have impairment across several cognitive domains, who may show greater neuropathology and an increased rate of progression to dementia.

Reitz and colleagues (2007) conducted a longitudinal analysis of 918 persons with MCI who were subdivided according to the amnestic (deficits in episodic memory) and nonamnestic (deficits in a non-memory domain) classification. They found that a history of hypertension was associated with increased incidence of MCI, and had a particularly strong association with non-amnestic MCI after controlling for age and gender. This relationship was attenuated after inclusion of stroke and vascular risk factors, suggesting that cerebrovascular disease may mediate this association. A similar issue was examined by He et al. (2009) in a cross-sectional study in which the MCI sample was divided into amnestic and nonamnestic subtypes. Persons with nonamnestic MCI were more likely to have cerebrovascular risk factors (i.e., stroke, transient ischemic attack, diabetes, hypertension, and coronary artery disease) compared to controls and persons with amnestic MCI. Risk factors for amnestic MCI include smaller hippocampi and the ApoE-4 allele, which is similar to findings in persons with AD.

The reasons for the differing associations between vascular factors and the different subtypes of MCI are unclear, but a popular theory involves the progression of the disease

underlying these entities. It has been suggested that the underlying pathology in amnestic MCI most closely resembles that seen in Alzheimer's disease whereas nonamnestic MCI participants exhibit pathologies different from those in Alzheimer's disease (He et al., 2009). Specifically, nonamnestic MCI may be more predictive of later vascular dementia (Reitz et al., 2007). While vascular dementia is inherently related to changes in the vascular system, the relationship between Alzheimer's disease and hypertension is less clear, with conflicting evidence regarding the magnitude of this relationship (Reitz et al., 2007). Further investigation of the relationship between hypertension and various subtypes of MCI and dementia must be undertaken to elucidate these links.

Heart Disease and Stroke

Vascular factors such as hypertension have been suggested to be associated with cognitive impairment due to decreased cardiac output and cerebral hypoperfusion, a common outcome of coronary heart disease (CHD; Roberts et al., 2010). Roberts and colleagues (2010) examined the association of CHD, defined by a history of myocardial infarction, angina, angiographic coronary stenosis, or coronary revascularization, with amnestic-MCI and nonamnestic-MCI. Participants with CHD had a 93% greater likelihood of nonamnestic-MCI than controls. There was no significantly increased risk of amnestic-MCI associated with CHD. Further, history of stroke, a more severe form of cerebrovascular disease, was associated with both forms of MCI, though this relationship was stronger in persons with the nonamnestic form. Similar results were found by Knopman and colleagues (2009) in a case-control design, with history of stroke being most strongly associated with deficits on the part B of the Trailmaking test (Reitan, 1958)

and the Digit Symbol Substitution test (Wechsler, 1981), both measures of executive function.

Mariani and colleagues (2007) also examined the prevalence of various vascular risk factors amongst participants with different forms of MCI in the ReGAI Project. Participants with nonamnestic single-domain MCI had a higher prevalence of ischemic heart disease, history of transient ischemic attack (TIA) or stroke, and white matter lesions found on MRI compared to those with amnestic single-domain MCI. Further, participants with multi-domain MCI (must have memory impairment) were more likely to have a history of stroke and TIA than those with amnestic MCI. The results of these studies lend support to the notion that the underlying pathologies involved in the amnestic and nonamnestic subtypes of cognitive impairment may be quite different, with cerebrovascular antecedents showing a greater effect on the likelihood of developing nonamnestic forms of MCI.

Diabetes Mellitus

Cerebral vascular disease, cardiovascular disease, and cerebral infarctions are also associated with presence of diabetes mellitus (Roberts et al., 2008). The duration and severity of diabetes mellitus has been associated with increased incidence of MCI, and has been suggested to be involved in the pathogenesis of cognitive impairment. Roberts and colleagues (2008) found that this association persisted even after adjusting for vascular factors, suggesting that diabetes mellitus may have an impact on cognitive function through other mechanisms in addition to its relationship with vasculature. This relationship may show differences in strength according to MCI subtype. Roberts and

colleagues reported significant associations of diabetes mellitus with nonamnestic MCI but not with amnestic MCI.

The authors suggest that deficits in insulin production may lead to increased amyloid plaque formation, which is associated with incidence of dementia, and particularly with Alzheimer's disease. Additionally, longstanding diabetes mellitus may be associated with cerebrovascular disease and cerebral infarctions, which may affect cognitive performance and is strongly associated with vascular dementia. A potential intermediary in this relationship is the presence of chronic hyperglycemia, which has been linked to cerebral damage and brain atrophy (Roberts et al., 2008). The strength of the relationship between diabetes mellitus and nonamnestic MCI, with its links to vascular dementia, suggest that this second path may be more likely to underlie this relationship. In a study of cognitive impairment in persons with diabetes mellitus, van den Berg and colleagues (2005) found an increased incidence of CIND but not amnestic MCI in persons with diabetes as compared to controls. Further, the cognitive impairment in the diabetes group was quite widespread, with nonmemory domains being most affected. This once again highlights the importance of using a broad definition of cognitive impairment, as its relationship with diabetes mellitus may not be as straightforward as previously thought.

Possible Mechanisms Underlying the Relationship Between Vascular Function and MCI

A potential mechanism underlying the relationship between vascular factors and MCI involves reduced glucose metabolism in the frontal lobes of persons with large volumes of white matter hyperintensities (WMHI), which may impact performance of the frontal-subcortical circuits (DeCarli et al., 2001). Although these circuits are not generally

thought to underlie episodic memory processes affected in amnestic MCI, they may impact performance on other cognitive tasks (i.e., executive functioning tasks) which may be impaired in nonamnestic subtypes of MCI (DeCarli et al., 2001). Furthermore, abnormalities or diseases of the vascular system are associated with accelerated white matter atrophy and reduced cerebral perfusion, which are all thought to lead to oxidative stress (Stephan, Matthews, Khaw, Dufouil, & Brayne, 2009). Oxidative stress has been linked to neurodegenerative disorders and amyloid pathology, and is one of the leading theories regarding the mechanisms of age- and neuropathology-related cognitive decline (Mecocci, 2004).

Hanon et al. (2005) suggest another potential mechanism underlying the association between vascular changes and MCI - arterial stiffening as measured by pulse wave velocity in the carotid artery. Arterial stiffness was also a predictor of both vascular dementia and AD. The authors suggest that cognitive deficits resulting from vascular factors may occur through increased central pulse pressure (the difference between systolic blood pressure and diastolic blood pressure in the carotid artery), resulting in arteriosclerosis, small infarcts, white matter lesions, and cortical brain atrophy. These have all been suggested as major risk factors for cognitive impairment, particularly when there is a large accumulation of pathology. Similarly, Kearney-Schwartz et al. (2009) reported that arterial stiffness in men was associated with memory impairments above and beyond the influence of other cardiovascular risk factors (e.g., blood pressure, presence of diabetes, cholesterol levels, etc.). further, stiffness was independently associated with severity of WMHI.

Objectives and Hypotheses

There are several limitations in the work conducted to date on vascular correlates of MCI. Many studies have used a cross-sectional design, which may be inadequate for examining within-person change in vascular function over time, and its association with cognitive decline. Null results from cross-sectional studies are often in conflict with evidence from longitudinal studies finding an association between vascular factors and MCI, suggesting that methodological issues may play a major role in results obtained (Reitz et al., 2007). Furthermore, the inconsistencies in defining MCI may have played a major role in the disputes in the literature, as noted above. Criteria for assessment of MCI have yet to be agreed upon, thus different research groups have operationalized it many ways (i.e., clinical complaints, neuropsychological testing, physician opinion, distributional approach), increasing confusion in this area. Many studies do not subdivide the MCI group into subtypes, and within those that do so, there are discrepancies in how the subtypes should be classified. To further complicate the issue, most studies have examined the role of physiological health in heterogeneous groups of persons with MCI, without differentiating those with stable MCI from those who decline cognitively over time. This may confound the problem, as these may be two distinct groups of persons, with different etiological and prognostic considerations. Finally, differences abound in types of vascular factors and covariates included in study design, as well as how these are operationalized. Despite these limitations, early detection and treatment of vascular abnormalities is hypothesized to be a key step in the delay or prevention of onset of MCI and dementia, and further work investigating these simple and noninvasive biomarkers is warranted (DeCarli et al., 2001).

To address these issues, a cross-sectional study is proposed to determine whether vascular functioning will be associated with cognitive impairment. This study will address vascular function by examining the following indicators of vascular health: Blood pressure, self-reported history of stroke, self-reported history of heart problems, and self-reported diagnosis of diabetes mellitus, both individually and together as an aggregate vascular factor. The association between vascular function as defined by these indicators and cognitive status will be examined, with participants classified into one of three groups: 1) single-domain CIND (sd-CIND), 2) multiple-domain CIND (md-CIND), or 3) not impaired cognitively (NIC).

It is expected that the individual vascular indicators will be related to cognitive status classification, with poorer vascular function being more strongly associated with sd-CIND and md-CIND as compared to the control group. Participants who are classified as not cognitively impaired area also expected to have lower incidence of problems with vascular function. Further, it is expected that examining the aggregate vascular factor in a multivariate approach will be more strongly associated with cognitive status than examining the vascular indicators individually, as this will provide richer information on vascular function by using multiple indicators to index functioning of the system.

Method

Participants

Data for this study were collected in the Victoria Longitudinal Study (VLS), a large-scale longitudinal, sequential study of community-dwelling older adults in Victoria, British Columbia. Participants in this study are tested every three years, and other general procedures utilized in data collection and analysis in the VLS are described elsewhere (see Dixon & de Frias, 2004). Data from three samples were utilized in this study, specifically Sample 1 (Wave 6), Sample 2 (Wave 4), and Sample 3 (Wave 1). Each sample consists of a different group of community-dwelling older adults living in Victoria, BC. Data was combined from the three samples to obtain a large enough sample size to evaluate the association of vascular function and cognitive impairment. Wave number corresponds to the number of times participants have undergone testing. It is of note that participants from Sample 1 (Wave 6) and Sample 2 (Wave 4) have already undergone several times of testing, and are likely to be more familiar with the measures used for cognitive classification than those from Sample 3 (Wave 1), for whom this is the first time of assessment. Exclusion criteria included history of significant head injury, Parkinson's disease, or epilepsy, and extensive drug or alcohol abuse. The initial sample consisted of n = 916 participants (608 women, 308 men). Participants were then divided into two age groups: a mid-old (MO) group (n = 436, 308 women, 128 men) with an age range from 53 to 71 years (M = 63.85, SD = 5.03) and an old-old (OO) group (n = 480, 300 women, 180 men) with an age range from 72 to 100 years (M = 79.38, SD = 4.83).

Cognitive Status Classification

The final sample was stratified into four groups based on a median-split of age (53 – 71 and 72 – 100) and education (0 – 12 years and 13 or more years), resulting in four subgroups. The subgroups were MO (low education) n = 76, MO (high education) n = 358, OO (low education) n = 114, and OO (high education) n = 359. A classification scheme for cognitive status based on work by Ritchie, Artero, & Touchon (2001) and Dixon et al. (2007) was used to classify participants as CIND or not-impaired cognitively (NIC) using cutoff scores of 1.5 standard deviations below the group mean. Other studies have used cut-offs of one standard deviation to delineate participants who are cognitively impaired, but this study utilizes 1.5 standard deviations due to the high education and good health status of the participants in the overall sample in the VLS. While this method of cognitive status classification has been extensively used in previous research, it must be noted that a limitation of the distributional approach is the lack of clinical judgment and diagnostic information in the classification of persons as CIND. However, by utilizing these cutoff scores within the sample distribution, we are utilizing a stringent approach to classification that may in fact show smaller effect sizes than would be expected using different classification methods. Specifically, the present classification scheme will delineate groups of persons with cognitive impairment whose scores are in the lowest seventh percent of the distribution.

Within-group means were calculated for five cognitive reference measures (described below) in the domains of perceptual speed, inductive reasoning, episodic memory, verbal fluency, and semantic memory. Participants scoring 1.5 or more standard deviations below their respective group mean on a single cognitive reference measure

were classified as sd-CIND, n = 148. Participants scoring 1.5 or more standard deviations below their respective group mean on two or more cognitive reference measures were classified as md-CIND, n = 65. All remaining participants who were not classified as CIND were assigned to the NIC group, n = 694.

Vascular Indicators

Blood Pressure and Hypertension

Eight measurements of blood pressure were taken at each testing time, with the participant sitting in a chair and relaxed prior to each measurement. An average of the eight measurements was calculated. Participants were categorized into 4 groups based on blood pressure readings: 1) Hypotension: average systolic blood pressure (SBP) less than 90 mmHg or average diastolic BP (DBP) less than 60 mmHg; 2) Normal blood pressure: average SBP between 90 and 119 mmHG and average DBP between 60 and 79 mmHG; 3) Prehypertension: average SBP between 120 and 139 mmHG or average DBP between 80 and 89 mmHg; and 4) Hypertension: average SBP greater than or equal to 140 mmHg or average DBP greater than or equal to 90 mmHg (Chobanian et al., 2003).

Stroke

Participants self-reported presence and severity (not serious, moderately serious, very serious) of a diagnosis of stroke by responding to the question “have you ever been diagnosed as having a stroke?”

Heart Troubles

Participants self-reported presence and severity (not serious, moderately serious, very serious) of heart troubles (examples given: congestive heart failure, angina, etc.) diagnosed by a medical practitioner.

Diabetes

Presence and severity (not serious, moderately serious, very serious) of diabetes was determined based on participants' self-report of a formal diagnosis by a physician. Participants also reported the type of diabetes that was diagnosed: diet-controlled, oral-medication-controlled, insulin-controlled or gestational.

Cognitive Reference Measures

Perceptual Speed

Perceptual speed was assessed using the Digit Symbol Substitution task from the Wechsler Adult Intelligence Scale Revised (Wechsler, 1981). Participants were asked to pair nine numbers (1 through 9) with nine random symbols using the key provided in the test. The number of correctly paired number-symbol dyads completed within ninety seconds was used as the outcome measure.

Inductive Reasoning

Inductive reasoning was assessed using the Letter Series test in which participants were required to examine a series of letters and provide the next letter according to a certain pattern that must be inferred from the presented letter string (Thurstone, 1962). The outcome measure was the correct number of letters provided in twenty trials.

Episodic Memory

Participants were presented with two lists, each consisting of 30 words, and were asked to freely recall the words (five minute time limit) after two minutes of studying each list (Hultsch, Hertzog, Dixon, & Small, 1998). The number of words correctly recalled was averaged across the two lists, and was used as the outcome measure.

Verbal Fluency

The similarities subtest of the Controlled Associations test (Educational Testing Services kit) was used a measure of verbal fluency (Ekstrom, French, Harman, & Dermen, 1976). This test required participants to generate as many synonyms as possible to four target words. Participants were given a total of six minutes to generate synonyms for all target words, which were presented at the same time. The total number of correct synonyms was used as a measure of verbal fluency. This test is somewhat different from other tests of verbal fluency, such as the letter fluency test, in which participants are required to name as many words as possible starting with a single letter within one minute without any cues (Spreen & Strauss, 1998).

Semantic Memory

Participants completed a 54-item multiple-choice vocabulary test from the Educational Testing Services kit with a time limit of fifteen minutes (Ekstrom et al., 1976). Participants were asked to select the word or phrase that was most similar in meaning to each target word, with five possible responses for each target word. The correct number of responses was used as the outcome measure.

Statistical Procedures

All statistical analyses were completed using PASW Statistics for Windows, Release Version 18.0 (SPSS Inc. Chicago, USA, 2009). The associations between all vascular factors and cognitive status groups were assessed using chi-square analyses. For all analyses, a p-value < 0.05 was considered significant. Proportions of participants in each cognitive status group at each level of the individual vascular indicators were calculated to provide descriptive information about the cognitive status groups.

Univariate analyses were then carried out using ordinal logistic analysis, a regression model that allows for categorical outcome variables with more than two levels. This approach was used as it assumes that the distance between levels of the outcome variables are not necessarily equal. This is of particular importance with regards to cognitive status classification as it is expected that person with sd- and md-CIND are likely to be more similar to one another than they are to persons with no cognitive impairment. Separate regression analyses were run for each of the four vascular indicators, with age and gender included as covariates in each model, to examine associations with cognitive status classification. One-tailed p-values were used to determine significance of association due to *a priori* hypotheses previously mentioned.

A multivariate approach using discriminant analysis was then used to determine if cognitive status group membership was associated with vascular function based on linear combinations of vascular indicators. Wilks' lambda was used as an indicator of differences in group means for each vascular marker. Values closer to 0 suggest that group means are quite different while values closer to 1 indicate little or no differences in group means

Results

Participant Characteristics

Following cognitive status classification, participants who did not have data for all four indicators of vascular function were excluded from the final sample to ensure equal sample size for comparison of analyses of each vascular indicator. The final sample consisted of 747 participants (487 women, 260 men), with the following cell sizes for each cognitive status group: sd-CIND n = 117, md-CIND n = 49, and NIC n = 581. The proportion of females and males in each group did not differ significantly, $\chi 2$ (2, N =747) = 3.89, p = .143. Two one-way analyses of variance (ANOVA) were conducted to evaluate group differences in age and years of education. No group differences were observed for age F(2,744) = 1.24, p = .289. Significant group differences were observed for years of education F(2,741) = 7.80, p = .009. Follow-up Tukey's HSD tests were conducted to evaluate pairwise differences among the means. The NIC group was found to have significantly more years of education than the sd-CIND group, p = .009 (see Table 1).

Table 1. Summary of participant characteristics.

	sd-CIND	md-CIND	NIC
Characteristic			
n	117	49	581
Age, mean (SD)	71.08 (9.15)	73.23 (10.29)	71.11 (9.02)
Sex, number	74 females	26 females	387 females
Education, mean (SD)	14.46 (2.83)	14.79 (3.09)	15.34 (2.95)

Note. SD = standard deviation.

Contingency Table Analysis

Four separate two-way contingency table analyses were conducted to evaluate homogeneity of proportions, that is, whether the proportions of individuals in each level of the four vascular indicators were the same for all cognitive status groups. In all analyses, cognitive status group with three levels (sd-CIND, md-CIND, and NIC) was included. In the first analysis, blood pressure classification with four levels (hypotension, normal, prehypertension, and hypertension) was evaluated with results indicating no statistically significant differences in proportions of individuals in the three cognitive status groups at each level of this vascular indicator, $\chi 2$ (6, N =747) = 3.69, p = .718. The second analysis revealed no statistically significant differences in proportions of individuals in each of three levels of stroke severity (none, not serious, and moderately serious), $\chi 2$ (4, N =747) = 5.26, p = .262. A third analysis evaluating differences in proportions of individuals in the three cognitive status groups at four levels of severity of heart problems (none, not serious, moderately serious, and very serious) indicated no

statistically significant differences, $\chi 2$ (6, N =747) = 6.47, p = .372. A final analysis revealed no statistically significant association of cognitive status group and severity of diabetes with three levels (none, not serious, and moderately serious), $\chi 2$ (4, N =747) = 4.11, p = .392. Taken together, these analyses indicated that there were no differences in proportions of individuals in each level of all four vascular indicators for the three cognitive status groups (see Table 2 for summary of counts and proportions).

Table 2. Classification of participants by cognitive status and levels of vascular indicators.

		Cognitive status		
		NIC	sd-CIND	md-CIND
BP classification	Hypotension	31 (5.3)	3 (2.6)	3 (6.1)
	Normal	161 (27.7)	36 (30.8)	17 (34.7)
	Prehypertension	293 (50.4)	57 (48.7)	20 (40.8)
	Hypertension	96 (16.5)	21 (17.9)	9 (10.4)
Severity of stroke	None	555 (95.5)	109 (93.2)	47 (95.9)
	Not serious	19 (3.3)	8 (6.8)	2 (4.1)
	Moderately serious	7 (1.2)	0 (0.0)	0 (0.0)
Severity of heart troubles	None	451 (77.6)	98 (83.8)	39 (79.6)
	Not serious	69 (11.9)	9 (7.7)	2 (4.1)
	Moderately serious	37 (6.4)	7 (6.0)	5 (10.2)
	Very serious	24 (4.1)	3 (2.6)	3 (6.1)
Severity of diabetes	None	542 (93.3)	107 (91.5)	42 (85.7)
	Not serious	21 (3.6)	6 (5.1)	4 (8.2)
	Moderately serious	18 (3.1)	4 (3.4)	3 (6.1)

Note. Count (Proportion of cognitive status group). NIC = not impaired cognitively. sd-CIND = single-domain CIND. md-CIND = multiple-domain CIND. Percentages may not add to 100% due to rounding error.

Ordinal Logistic Regression

Four separate univariate ordinal logistic regression analyses were conducted to evaluate the association of cognitive status classification with each measure of vascular function, including age and gender as covariates in each analysis. Severity of stroke was significantly associated with cognitive status classification based on the one-tailed *p*-value of the omnibus test of model fit, $p = .040$. The parameter estimate for a one unit increase in stroke from no history of stroke to history of mild stroke was significantly associated with cognitive status classification, $p < .001$. The association of cognitive status and severity of heart troubles approached significance in the omnibus test of overall model fit, $p = .056$. However the individual parameter estimate for severity of heart troubles was not significant. Neither BP classification nor severity of diabetes were found to be significantly associated with cognitive status classification based on omnibus tests of model fit, $p = .135$ for BP classification and $p = .120$ for severity of diabetes. These results indicated that the regression model including BP classification and severity of diabetes was not significantly better than the model without these indicators; therefore individual coefficients should not be evaluated.

Discriminant Analysis

A discriminant analysis was conducted to determine whether four vascular indicators – BP classification, severity of stroke, severity of heart troubles, and severity of diabetes – would be associated with cognitive status classification. The overall Wilks' lambda was not significant, $\Lambda = .99$, $\chi 2\ (8, N = 747) = 6.51$, $p = .590$, indicating that overall the indicators did not differentiate among the three cognitive status groups. As this test was not significant, the discriminant function could not be interpreted.

Discussion

The primary goal of this study was to examine the relationship between indicators of vascular function and cognitive impairment. We were specifically interested in the association of cognitive status classification (sd-CIND, md-CIND or NIC) and individual measures of vascular function, as well as an aggregate vascular factor comprised of all indicators. Contrary to expected results, we did not find a significant association between any of the vascular indicators (i.e., blood pressure classification, severity of stroke, severity of heart troubles, and severity of diabetes) and the cognitive status classifications. Further, group membership was not associated with any of the individual vascular markers, or with a multivariate combination of the indicators.

How do the Results of This Study Relate to Previous Research?

While the results of this study are not consistent with our hypotheses, there are also several studies in the literature that have failed to document significant associations between vascular function and MCI. This suggests that the relationship is not simple and straightforward, particularly in light of the nature of the sample in the VLS, as will be discussed below. In a longitudinal study examining the relationship between blood pressure and risk of AD, Morris and colleagues (2001) found high blood pressure levels measured 13 years before, four years before, and two years after onset of AD did not increase one's risk of developing this disorder. Similarly, Johnson and colleagues (2008) did not find significant evidence of the relationship between high blood pressure and MCI or probable dementia in a group of older women after controlling for various covariates such as age, education, ethnicity, smoking status, alcohol intake, body mass

index, physical activity, and presence of depressive symptoms. Of particular importance in this attenuation effect was the inclusion of age and ethnicity in the analyses. Both groups suggest that some of the discrepancies in the literature may be associated with differences in study designs, especially in the selection of which covariates are included in the analyses. Many studies do not include covariates such as age, years of education, and gender in analyses, even though these are often thought to be strongly associated with incidence of MCI and of dementia. Inclusion of these potential confounds may strongly influence results obtained in previous studies, and may account for a great deal of the variability in results observed.

There is a widespread debate in the literature regarding the time course of the relationships between elevated blood pressure and risk of MCI. While many studies have investigated the relationship between late-life problems with vascular function and cognitive function, others have argued that it may be more appropriate to examine this relationship over a longer period of time (DeCarli et al., 2001; Kivipelto et al., 2001). In a systematic review including 13 studies, van den Berg (2009) examined the relationship between hypertension and dementia, and found discrepant results based on the developmental stage at which blood pressure was assessed. In all five studies examining blood pressure at midlife, there was a significantly increased risk of developing dementia later in life associated with elevated blood pressure. However, only one (of nine) studies examining blood pressure in late life found an increased risk of dementia associated with high blood pressure. This suggests that late-life measures of blood pressure may not be as sensitive in predicting cognitive decline as midlife measures, which are likely indicative of more long-standing deficits in vascular function.

General factors that lead to systematic hypertension may be manifest in atherosclerosis and ischemia of vessels servicing the brain, which may increase risk of developing MCI or dementia over a long period of time (Kivipelto et al., 2001). Further, midlife elevations in blood pressure have been found to predict later-life WMHI volume (DeCarli et al., 1999), also associated with decreased performance on various cognitive measures assessing attention, memory, and verbal fluency (DeCarli et al., 2001). This may be an explanation for the mixed results in studies measuring blood pressure in late life, as the consequences of reduced cerebral blood flow may not yet be present if there has not been sufficient time for WMHI to form. While the aforementioned studies investigated measures of blood pressure at midlife, it is also possible that similar findings would be expected in comparing midlife and late-life measures of other vascular indicators, such as stroke, heart problems, and diabetes (cf. Roberts et al., 2008). As this study used measures of vascular function taken at the same time as assessment of cognitive status, there may be a lower likelihood of finding a significant association as we do not have information on long-term vascular function. This suggests the need for future research using a longitudinal study design.

What is the Influence of Study Design on the Results of This Study?

As discussed in earlier sections, one of the greatest difficulties in interpreting and comparing results from various studies is the large discrepancies in definitions of MCI. There are both theoretical differences in conceptualizing MCI as an entity, as well as practical differences in how this group is defined in a particular study. Many definitions of MCI include self-reported complaints of memory disturbances, which lead to an impaired sample with memory deficits who are more likely to transition to AD than other

types of dementia (Petersen et al., 1999). This group of persons with cognitive impairment may be quite different from an impaired sample defined as CIND whereby impairment is more broadly defined as deficits in several possible domains (i.e., executive functioning, language, attention, memory). Non-amnestic forms of cognitive impairment may be more related to other forms of dementia, especially vascular dementia, and are likely to show stronger relationships with vascular predictors (Reitz et al., 2007).

In the current sample, we were unable to divide the cognitive impairment group according to an amnestic or non-amnestic classification scheme due to small cell size. As we made use of the more encompassing CIND criteria, our cognitively impaired sample is likely more heterogeneous than a group that is classified according to Pertersen et al's (1999) criteria. While these will likely lead to greater interindividual variability, we chose to employ these methods to include persons with non-amnestic forms of impairment, who may be on the trajectory to non-AD forms of dementia. As previously stated, there is evidence suggesting that non-amnestic forms of MCI are actually more associated with changes in vascular function (Reitz et al., 2007). Further, the use of CIND criteria is more descriptive, and may be more accurately representative of cognitive impairment in the population who do show great differences in cognitive domains affected by the disease process (Backman et al, 2005).

A further limitation of the distributional approach used for classifying cognitive status is that it is intrinsically related to the particular sample to which it is applied. In this case, as the Victoria Longitudinal Study is not a true representative sample of the population of older adults in Canada, there may be some limitations to the

generalizability of the results obtained using data from this study. For instance, the average years of education of participants in this study ranged from 14.46 years for sd-CIND to 15.34 years for NIC, which is quite similar across groups, but very different from the national average for older adults in Canada. According to data from Statistics Canada (2006), only 16% of older adults aged 65 to 74 years and 12% of older adults aged 75 and over in Canada have obtained a University certificate, diploma, or degree. This suggests that the average number of years of education among older adults is substantially lower than the average educational attainment of participants in the VLS.

It is of particular importance to note that the average years of education in both CIND groups are extremely high, which has many implications for the interpretations of how impairment is defined in these groups. By using a distributional approach with 1.5 SD cut-offs for impairment, we are forcibly assigning a certain percentage of the sample to the cognitively impaired group as these persons are at the low end of the distribution of scores in this sample. However, with a sample with very high education, persons in the lower end of the distribution may be considered "impaired" relative to others in the sample, but may still perform within an average range when compared to the general population. Without the inclusion of clinical judgment, there is less certainty that our cognitive impaired groups are performing below their expected level, and that they are truly impaired. We should be cautious in our interpretation of the null results in this sample where cognitive status is determined by group norms, and that group has very high overall educational attainment.

An additional limitation of the present study is the use of a cross-sectional design to evaluate the association of vascular function and cognitive status. Hofer and Sliwinski

(2001) argue that cross-sectional designs with age-heterogeneous participants will likely positively bias estimates of processes that exhibit changes over time. In these types of studies, we generally examine relationships between average trends among individuals of different ages which may result in inflated estimates of shared variance of age-related processes. While this was not the case in this particular study, the limitations of cross-sectional designs must be kept in mind when planning follow-up studies to avoid this potential outcome. The authors suggest alternative approaches that are more appropriate for investigating associations among age-related effects in different processes, such as narrow age cohort design. Under the guise of this type of design, participants are chosen within a small age range, thereby decreasing or even eliminating the mean age effect.

Alternatively, longitudinal studies may provide the strongest supporting evidence for associations between age and various processes. Others have argued that longitudinal studies are also problematic as they are based on a single cohort, may not be representative of the population, and must deal with the effect of practice. (Salthouse, & Nesselroade, 2002). While this latter point is less of a concern for measures of physiological function, it can be a major factor for the tests that are used to define our cognitive status groups. That is, there may be practice effects for cognitive tests used for defining MCI, which would in turn make it more difficult to determine which participants are exhibiting cognitive decline over time. However, many of these issues must also be addressed in cross-sectional studies, and Hofer, Sliwinski, and Flaherty (2002) argue that longitudinal analyses can address many of the limitations of cross-sectional designs and provide a method of distinguishing systematic and unsystematic variances in performance over time. While we were unable to employ longitudinal techniques in the current study,

follow-up studies would benefit from the use of such designs to overcome the limitations of cross-sectional analyses.

A further difficulty in conducting cross-sectional studies investigating MCI is the issue of stability of classification, and particularly the inconsistent trajectories in persons classified as MCI (Vandermorris et al., 2010). While MCI is often seen as a precursor to dementia, falling between normal cognitive function and decline to diagnosis of dementia, there is great variability in conversion rates, with annual conversion rates ranging from 1% to 40%. These rates depend on the study, criteria used to assess both MCI and dementia, and the demographic variables included in analyses (Palmer, Fratiglioni, & Winblad, 2003). Further, an issue that causes great difficulty in ensuring reliability of cognitive status classification is the high rate of reversion from MCI to cognitively intact over time, that is, persons who are classified as cognitively impaired at time 1, but are then found to have normal levels of cognitive function at time 2. Some groups have suggested that the reversion rate may be up to 40% over a course of two or three years, indicating very poor stability of classification (Fabrigoule, Barberger-Gateau, & Dargiues, 2006; Ritchie, Artero, & Touchon, 2001). Vandermorris and colleagues (2011) have suggested that a more appropriate classification scheme for MCI should include persistence of impairment over time, lending support to continued impairment over time. The authors found a high rate of reversion (i.e., 41%) over a period of five years, and argue that the criteria used for defining MCI should be revised to include persistency of impairment. Including stability of classification in our definitions of MCI would likely lead to greater ability to identify those at greatest risk of declining due to

diagnosis of dementia, and may improve our ability to create sensitive markers of cognitive decline.

However, it is of importance to note that stability of classification was examined as an additional step in this study, with results that are quite discrepant from the literature on reversion rates. It was found that cognitive status classification was highly stable in this sample when participants were reclassified into cognitive status groups at time 2, three to six years following testing at time 1. Specifically, all 581 participants classified as NIC remained NIC at time 2, 40 participants remained stable in their CIND classification, and four participants declined from sd-CIND to md-CIND three to six years after testing at time 1. An initial goal of the current study was to examine changes in vascular function associated with changes in cognitive status over time; however, we were unable to do so due to the lack of change in cognitive status over time. The stability of classification in this sample is extremely high compared to other studies, and it will be very interesting for further work to investigate the factors associated with this stability.

There are several possible explanations for the stability of cognitive status over time in this particular sample, including the overall high functioning of this group, high education and SES, low base rate of disease, and short follow-up time. Additionally, the lack of clinical judgment in the classification scheme for MCI in this particular study, combined with the above-average nature of VLS participants, may further increase the difficulty in identifying changes in cognitive function over time. It may be of great interest to examine change in performance on various cognitive tasks, rather than just change in classification status, as it is possible that the classification scheme used to identify persons as MCI may not be sensitive enough to identify small changes in

cognitive functioning. It would be interesting in future studies to utilize several different classification schemes to determine if other methods of defining cognitive status are more sensitive to changes in performance and reduce stability of classification over time.

An additional issue to consider in the lack of decline found in this sample is the influence of practice effects, especially over a short period of time between times of testing. Within most longitudinal designs, there is a potential confound between effect of repeated testing and changes in cognitive function over time, particularly declines associated with age or disease processes (Thorvaldsson, Hofer, Berg, & Johnsson, 2006). Retest and practice effects are thought to influence performance on various cognitive tasks over time, though there is dispute in the literature as to which cognitive domains are particularly affected. For instance, Wilson, Li, Bienias, and Bennett (2006) found strong retest effects for measures assessing semantic memory, while others have found stronger retest effects for measures of episodic memory (Ronnlund et al., 2005). This may be of particular importance in studies such as this, where classification of cognitive status employs a distributional approach with scores on tests representing various cognitive domains.

As we are utilizing performance on specific measures to classify persons as cognitively impaired, there may be greater error in classification over several periods of time due to the conflicting influences of practice effects and the aging or disease process. For example, in this particular study, performance on Letter Series task was used as a measure of inductive reasoning and was included in the classification scheme for cognitive status (Thurstone, 1962). As participants included in this study from Sample 1 (Wave 6) and Sample 2 (Wave 4) had already completed multiple points of testing, there

is a possibility that their scores on this measure are inflated compared to what they would be if this was the first time they were assessed or compared to participants from Sample 3 (Wave 1) who are doing this test for the first time. If these participants did show practice effects on this particular measure, they would be less likely to perform on the lower end of the distribution of scores within the overall group, and would thereby be less likely to be classified as impaired in this cognitive domain. In this way, practice effects can have influence on cross-sectional designs within longitudinal studies when participants have had prior exposure to testing stimuli. While this issue has less influence on studies that are cross-sectional in nature, proposed follow-up studies that utilize longitudinal analyses must take these into consideration.

What is the Impact of Education on the Association of Vascular Function and Cognitive Status?

Many studies have found results indicating that increased years of education in early life reduce risk of developing dementia in later life (Ott et al., 1995; Stern, Albert, Tanh, & Tsai, 1999). While there is debate regarding the mechanism underlying the role of this protective factor, recent work suggests that greater educational attainment may increase cognitive reserve, which in turn allows for greater resilience against neuropathology (Brayne et al., 2010). Evidence from a population-based sample demonstrated that highly educated older adults were less likely to develop dementia compared to their less-educated peers. However, highly educated adults did not have less neurodegenerative or vascular pathologies than less-educated older adults, suggesting that more education does not protect individuals from developing brain pathology, but rather may help decrease the impact of the neurodegeneration on cognitive function. The

authors suggest that this relationship is likely further strengthened by associations with socioeconomic status (SES), whereby persons with more years of education are more likely to have a higher SES. Further, low SES has been associated with increased risk of cardiovascular disease (Clark et al., 2009). For example, Avendano and colleagues (2006) found an increased risk of stroke in older adults aged 64 to 75 years associated with fewer years of education and lower income, both indicators of low SES.

This has important implications for the current study, as this sample is highly educated, and is likely to have a generally high SES, which may, in part, be a contributing factor to the null results described above. As persons with higher SES are less likely to have problems with vascular function, the lack of association between vascular function and cognitive status in this study may be strongly related to educational attainment of participants. This may also be a part of the explanation for the results of the contingency table analyses where participants in all groups showed very similar proportions of persons at each level of the vascular indicators. This may also be indicative of low sensitivity in our approach used for cognitive status classification. Specifically, there was a very low base rate of problems with vascular function across all three cognitive status groups, indicating that this group is indeed very healthy and high functioning, and less likely to show a strong association between vascular problems and cognitive impairment.

This suggestion is strengthened by ordinal logistic regressions that were run as a follow-up to this study in which education was also included as a covariate in the three separate regression analyses for blood pressure classification, severity of heart troubles, and severity of diabetes. In these analyses, the models did in fact reach significance,

suggesting an association between vascular function and cognitive status. However, upon further investigation of the parameter estimates in these models, the only factor that was significantly associated with cognitive status was years of education. The strong association of education with cognitive status suggests that education is driving this association, rather than disease status.

Future Directions

While the results of the current study did not show the pattern of results that was expected, several potential reasons were previously presented which may account for this discrepancy. Several follow-up studies are suggested to further elucidate the association between vascular function and MCI. First, as the VLS is a longitudinal study with many time points of assessment, the next step in this series of studies would make use of the available longitudinal data. An advantage of this approach is the ability to use multiple measurement times in the classification of cognitive status, which will likely be a more reliable indicator of cognitive impairment compared to a single assessment point (Vandemorris et al., 2011). It would be interesting to evaluate the utility of several methods of defining cognitive status groups, which can help determine which approach is most sensitive to changes in vascular function over time.

Additionally, we will be able to follow participants over a long period of time, which may provide information on changes in vascular function over time that we were unable to ascertain in the additional analyses using only one point of data. Ideally, we would include a minimum of three time points, and hopefully additional time points if possible, that will allow us to model change in both cognitive and vascular function over an extended time. This approach would also allow for the use of sophisticated statistical

techniques incorporating a multivariate approach with both growth modeling and survival analysis. In this study, a growth model will be fit in which a continuous latent variable, comprising the vascular indicators, is modeled to examine development of individuals over time. Within this framework, a structural equation modeling approach will be taken whereby the growth function can be estimated as a function of time. Discrete time survival analyses will be used to evaluate hazards of group membership and cognitive status stability as a function of change in the latent vascular factor. It is anticipated that decreasing vascular function will be associated with a greater hazard of cognitive impairment. Worsening vascular function is also expected to be associated with increased risk of transitioning from non-impaired to MCI.

As previously mentioned, late-life markers of vascular function may not be as sensitive predictors of cognitive impairment as midlife markers, which is an empirical question that could be addressed using Sample 1 data that was collected across 7 waves, with 3 years between each time of testing. An important issue to evaluate is whether vascular function at time 1 is more predictive of cognitive function later in life than vascular function assessed at the time of cognitive status classification. This may help provide some clarity in the debate on use of midlife or late-life markers of vascular function, and may provide great clinical utility for future development of simple, non-invasive measures of biofunction that are sensitive to risk of cognitive decline. It is of great interest to determine whether changes in vascular functioning will result in change in cognitive status, particularly a decline from NIC to CIND, and from sd-CIND to md-CIND. If change in vascular indicators is highly sensitive to changes in cognition, these

may provide very useful information on important physiological interventions that could be used to decrease risk of cognitive decline over time.

Conclusions

The results of this study did not find a significant association between markers of vascular function and cognitive status classification, specifically differences among participants classified as NIC, sd-CIND, or md-CIND. These results are inconsistent with our expected findings; however, there is precedent in the literature for null results in this area of research. There are several possible reasons for this study's findings. Firstly, there is are numerous ways to define MCI, and the particular classification scheme used in this study for CIND may have yielded more heterogeneous groups with greater variability in vascular function, thereby obfuscating an association with cognitive status. Secondly, various characteristics of the sample used in this study may have influenced the null findings, including the overall high functioning of the group, low base rate of vascular problems, and high education. Years of education was found to be associated with cognitive status in subsequent analyses, and may be a major confound in this study as all cognitive status groups had a very high average educational attainment. Thirdly, this study was cross-sectional in design and may not be the most appropriate design for understanding the relationship between vascular function and MCI, though inflated findings were not apparent in this study. Future directions for research in this area should utilize a longitudinal approach to evaluating this relationship, whereby participants are assessed over multiple time points to provide rich information on changes in cognition and vascular function. This will allow us to investigate both the relationship of midlife vascular function on late-life cognitive deficits, as well as the relationship of change in

vascular function over several years to changes in cognitive function over the same period of time.

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