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The Role of Lifestyle Factors in Cognitive Aging and Dementia

Tiffany F. Hughes
University of South Florida

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by

Tiffany F. Hughes

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Co-Major Professor: Brent J. Small, Ph.D.
Co-Major Professor: Ross Andel, Ph.D.
Cathy L. McEvoy, Ph.D.
James A. Mortimer, Ph.D.
Huntington Potter, Ph.D.

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ABSTRACT

It is widely accepted that cognitive abilities decline with normal aging. At the same time it is also recognized that there is variability in the magnitude and rate of decline among aging individuals. A similar phenomenon exists for dementia, where individuals with similar neuropathologic burden present with varying degrees of cognitive impairment. Of importance is determining what factors account for this variability, and whether individuals can modify these factors in order to preserve their cognitive abilities with aging or delay the onset of dementia.

The purpose of this dissertation was to examine three potentially modifiable lifestyle factors' association with age-related differences/change in cognitive performance and risk for dementia by conducting three separate studies. The first study examined the association between engagement in lifestyle activities and concurrent cognitive speed performance. The second study examined whether there are differential associations between social resource factors and change in cognitive performance. The final study estimated the risk of late-life dementia in Swedish twins as a function of fruit and vegetable consumption in midlife.

Taken together, the results of these studies provide evidence that individuals may be able to protect themselves against age-related cognitive decline or dementia by modifying their lifestyle. Specifically, individuals may benefit their cognitive speed

performance by engaging in more cognitively demanding activities. Declines in episodic memory performance may be alleviated by being more satisfied with social support, and declines in general cognitive performance and speed and attention in young-old adults may be attenuated by having a larger social network of friends. Finally, the risk of all types of dementia and Alzheimer's disease may be reduced by consuming a moderate amount of fruits and vegetables in the diet, especially for females, those with self-reported angina, and those who consumed alcohol in midlife. These findings contribute to the literature on potential strategies to maintain cognitive health with aging and serve as groundwork for future intervention studies.

Preface

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Chapter One: Introduction

The study of determinants of successful cognitive aging is receiving increased attention as research demonstrates that there is considerable heterogeneity in the magnitude of and rate of cognitive change experienced by older adults (Christensen, 2001). While some individuals remain relatively cognitively intact into old age, others become cognitively impaired, suggesting that cognitive decline or impairment is not an inevitable part of aging. As we approach a time where older adults will comprise a larger portion of the total population, a clearer understanding of what factors modify age-associated and pathological changes in cognition is necessary in order for older adults to maintain cognitive health with aging.

Research now supports that both genetic and environmental factors contribute to age-associated changes in cognition and to dementia risk (Finkel & Pedersen, 2004; Gatz, Reynolds, Fratiglioni, Johansson, Mortimer, Berg, et al., 2006). Throughout the life course various factors including genetic (Ashford & Mortimer, 2002; Farrer, Cupples, Haines, Hyman, Kukull, Mayeux et al., 1997; Finkel & Pedersen, 2004; Plomin, 1999), demographic (Anstey, 2000; Katzman, 1993), health (Anstey, 2000; Christensen, Jorm, Henderson, Mackinnon, Korten, & Scott, 1994; Rosnick, Small, McEvoy, Borenstein, & Mortimer 2004), and lifestyle factors (Crowe, Andel, Pedersen, Johansson, & Gatz, 2003; Fratiglioni, Paillard-Borg, & Winblad, 2004; Fritsch, Smyth, Debanne, Petot, & Friedland, 2005; Hultsch, Hammer, & Small, 1993; Hultsch, Hertzog, Small, & Dixon, 1999; Small, Hughes, Hultsch, & Dixon, 2007) interact to either protect against or

increase susceptibility for cognitive decline or dementia. Although cognitive decline and dementia manifest in old age, the current demographic trends in the aging population demand that interventions in mid- and late-life be elucidated. The current dissertation focuses on how environmental factors in mid- and late-life are associated with cognitive functioning in non-demented individuals and with risk for dementia. Specifically, the dissertation examines three environmental factors; lifestyle activities, social resources, and fruit and vegetable consumption and their associations with age-related differences/changes in cognitive functioning and with dementia risk. The ability of these factors to modify age-related differences/changes and dementia risk is examined within the framework of the environmental complexity and cognitive reserve hypotheses.

Considerable interest now exists regarding whether engagement in lifestyle activities can decrease risk for cognitive decline or dementia. Since participation in lifestyle activities is potentially modifiable even in mid- and late-life, the implications of the research findings could be profound. Unfortunately, the existing body of literature on the association between engagement in lifestyle activities and cognition is mixed. Several issues related to the measurement of lifestyle activities, their association with different domains of cognitive functioning, and the directionality of the association between lifestyle activities and cognitive performance have contributed to the inconsistencies in the literature (Small et al., 2007). In addition, few studies have examined whether lifestyle activities are associated with variability in cognitive performance, which may be more indicative than mean level performance of how lifestyle activities affect the integrity of the central nervous system (Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Li, & Lindenberger, 1999).

A substantial body of literature suggests that social resources are associated with physical and mental health outcomes (Seeman & Crimmins, 2001). Recently, social resources have begun to be examined for their potential association with cognitive functioning. Various aspects of social resources, such as social network (Holtzman, Rebok, Saczynski, Kouzis, Wilcox Doyle, & Eaton, 2004) and social support (Seeman, Lusignolo, Albert, & Berkman, 2001), have been found to be associated with cognitive functioning. However, there are inconsistencies in the literature when different types of social resources are examined and associated with different cognitive outcomes. Determining whether different aspects of social resources, such as social network or satisfaction with social support, are more beneficial to cognitive functioning than others is important for older adults' maintenance of cognitive abilities.

It is known that proper nutrition is an important factor in the promotion of cognitive health with aging (Fillett, Butler, O'Connell, Albert, Birren, Cotman, et al., 2002), but the extent to which nutrition-related factors affect the risk for cognitive impairment in old age remains to be elucidated (Gonzalez-Gross, Marcos, & Pietrzik, 2001). Although studies have shown that dietary intake of specific macro- and micro-nutrients are associated with risk for dementia (see Gillette Guyonnet, Abellan Van Kan, Andrieu, Barberger Gateau, Berr, Bonnefoy, et al., 2007 for review), there is limited evidence regarding the associations between fruit and vegetable consumption and dementia that "reflect the effects of dietary exposures and not changes in diet secondary to the disease" (Luchsinger & Mayeux, 2004, p.580). In addition, to our knowledge no studies have examined the risk for dementia in twins to account for genetic and early-life factors.

The development of strategies that may reduce risk for cognitive decline or dementia hinges upon research that examines factors that are malleable in mid- and late-life. The present doctoral dissertation focuses on lifestyle activities and social resources in late-life as potential strategies to mitigate age-related differences or to slow age-related cognitive decline, and on fruit and vegetable consumption in midlife as a potential strategy to reduce risk for dementia. The dissertation is organized as three individual studies with the overarching theme reflecting environmental (leisure activities, social resources, and diet) predictors of cognitive performance and cognitive impairment. The first study examines whether lifestyle activities influence older adults' mean-level performance and variability on measures of cognitive speed. The second study assesses the association between seven aspects of social resources; social network of family, social network of friends, instrumental support, emotional support, informational support, satisfaction with support, and negative interactions, and performance on a battery of cognitive tests including global ability, attention and perceptual speed, and episodic memory at baseline and over five years. Finally, the third study examines fruit and vegetable consumption assessed prospectively in midlife and risk for dementia controlling for potential confounds including early environmental factors and genetic background by using a sub-sample composed exclusively of complete twin pairs.

The following chapter is a review of the existing body of literature on cognitive functioning with aging and dementia and factors that potentially influence cognitive health in old age.

Chapter Two: Literature Review

A key determinant of successful aging is maintaining cognitive functioning (Baltes & Baltes, 1990). Maintaining cognitive abilities with aging is important for older adults to perform the activities of daily living that are necessary for independent living; therefore understanding ways in which cognitive functioning is maintained or cognitive impairment can be delayed or prevented is crucial for older adults' quality of life. The overarching theme of the dissertation is to explore environmental factors that contribute to successful cognitive aging in older adults. First, what is currently known about normative age-related changes and changes associated with dementia, the study outcomes of the dissertation, is reviewed. Two theoretical models that attempt to account for the link between environmental factors and cognitive functioning and dementia risk are then discussed. Finally, the factors currently under investigation for their association with differences/change in cognitive functioning and with risk for dementia are described.

Cognitive Functioning and Aging

Normal Aging

Despite disagreement about the nature and extent of change in cognitive functioning across the lifespan (Christensen, Mackinnon, Jorm, Henderson, Scott, & Korten, 1994), it is generally accepted that there are declines across multiple cognitive abilities, regardless of testing in lab or real world settings (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004; Wilson, Beckett, Barnes, Schneider, Bach, Evans, et al., 2002). The declines are not unitary across cognitive domains, however (Park, 2000).

During the course of adult development two patterns of change in cognitive functioning are evident. Some abilities have been shown to remain relatively stable into old age, while others follow a trajectory of decline (Baltes, Staudinger, & Lindenberg, 1999; Horn & Cattell, 1966; Horn & Hofer, 1992; Salthouse, 1999). The abilities that show stability are known as crystallized abilities. Verbal abilities, including vocabulary, information, and comprehension are considered to be crystallized. Abilities such as speed of processing, memory, spatial ability, and reasoning are those that tend to decline with aging and are known as fluid abilities. Different mechanisms have been proposed to explain age-related declines in cognitive performance. These mechanisms include, but may not be limited to, the processing speed theory, working memory, inhibition and sensory function (Park, 2000). These processes, especially processing speed, often account for a large proportion of age-related variance across a wide assortment of tasks and environments, but are rarely able to entirely eliminate age-related differences in cognitive functioning.

A great deal of research on cognitive aging has focused on age differences in cognition. This is primarily the result of the use of cross-sectional study designs which are faster and less expensive to conduct. Most cross-sectional studies of cognitive aging have reported that older adults perform more poorly than younger adults on most cognitive tasks, with the exception of vocabulary performance (Park, 2000). This was supported by Park, Smith, Lautenschlager, Earles, Frieske, Zwahr, et al. (1996) who found that cognitive performance on tasks of processing speed, working memory, and cued and free recall all declined in a generally linear pattern across the lifespan from age 20 to age 90 . In contrast, vocabulary performance was found to remain relatively stable

across the lifespan. Cross-sectional studies of older adults also find that young-old adults perform better than old-old adults on cognitive measures. For example, Christensen and colleagues (1994b) found age differences between the 70-74, 75-79, and 80 and over age groups in crystallized intelligence, fluid intelligence, and memory where there was a decrease in performance across the age groups. In their study, fluid abilities were found to decline more than crystallized abilities as a function of age, and all individual tests were found to show decline with the exception of vocabulary. The results of these studies demonstrate that age differences in cognition exist even into very old age. However, an accurate description of cognitive aging requires that change in cognition be examined through longitudinal methods, which are able to estimate individual rates of decline or risk factors for decline, and can examine the association between changes in cognitive functioning and changes in other cognitive and non-cognitive domains (Christensen, 2001).

In order to better understand what normal cognitive changes can be expected with aging and to discover the mechanisms that explain adult development, researchers are now recognizing the importance of longitudinal studies of aging (Schaie & Hofer, 2001). Wilson and colleagues (2002) examined cognitive changes on 21 cognitive tasks consisting of the domains of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability over six years in a cognitively intact sample of older adults. They found that performance on each of the cognitive domains declined over the 6-year period and that the rate of decline in each domain was related to age at baseline such that those who were older experienced greater declines. Moreover, the authors also found that there was substantial heterogeneity in each of the cognitive

domains, indicating that while on average there are declines, some older adults remain stable or improve slightly over time as well. It has not been until recently that longitudinal studies of cognitive aging have examined change into very old age. A study conducted by Singer, Verhaeghen, Ghisletta, Lindenberger, and Baltes (2003) examined change in four intellectual abilities (i.e. perceptual speed, memory, fluency, and knowledge) over six years in a sample of adults ranging between 70 and 100 years of age from the Berlin Aging Study. Overall, the results of their analyses showed declines with age in perceptual speed, memory, and fluency. Performance on the knowledge tasks (Vocabulary and Spot-the-Word), however, remained stable until age 90, but declined thereafter. Despite the advantages provided by longitudinal studies of cognitive aging compared to cross-sectional studies, it is important to consider issues such as attrition, survival effects, missing data, and practice effects when interpreting the results of longitudinal studies (Schaie & Hofer, 2001).

Cognitive differences/changes associated with normal aging can vary both between and within older adults with regard to the magnitude (Bäckman, Small, & Wahlin, 2001) and rate (Wilson et al., 2002) of decline. There is evidence that both between- and within-person variability increases with normal aging. Between-person variability refers to the fact that individuals begin and end at different places on tests of cognitive performance. By contrast, within-person variability refers to the fact that persons may perform differently from day to day, as well as from trial to trial. For example, Hultsch, MacDonald, & Dixon, (2002) found that cognitive performance on reaction time tasks became increasingly more diverse, dispersed, and inconsistent with age, and that these measures were positively associated with each other and negatively

associated with performance on other cognitive composites. Although the majority of research on variability in cognitive functioning in older age has focused on between-person variability, or diversity, there is increasing interest in the study of within-person variability in the study of cognitive performance.

Two types of within-person change that have been described are intraindividual change and intraindividual variability (MacDonald, Hultsch, & Dixon, 2003). Intraindividual change refers to change that is relatively slow and enduring (e.g. learning, development, and changes in traits), while intraindividual variability refers to change that is relatively rapid and transient (e.g. mood states, emotions, and fluctuations in performance). Variability associated with a person's performance on multiple cognitive tasks is known as dispersion, whereas variability associated with a person's performance on a single task measured on multiple occasions is referred to as inconsistency (Hultsch et al., 2002). Traditionally, performance inconsistency was regarded as random error (Williams, Hultsch, Strauss, Hunter, & Tannock, 2005); however recent studies have shown that inconsistency is not a statistical artifact and can be measured reliably apart from other within-person variability (e.g. practice effects, learning to learn, materials effects) (as cited by Hultsch et al., 2000). Since inconsistency has been shown to predict cognitive performance independently of mean level performance, and also to predict mean level change, performance variability may be a useful behavioral indictor in addition to mean level performance (Hultsch et al., 2000; Hultsch et al., 2002; MacDonald, Hultsch, & Dixon, 2003; Williams et al., 2005).

Dementia (with focus on Alzheimer's disease)

Alzheimer's disease is characterized by a progressive loss of intellectual and cognitive functioning that ultimately impairs everyday functional abilities (Sloane, Zimmerman, Suchindran, Reed, Wang, Boustani, et al., 2002). In the mild stages of the disease, patients generally suffer from memory loss and may have some difficulty with executive functions, language, and attention (Sloane et al., 2002). This is consistent with the diagnostic criteria of impairment in memory plus an additional cognitive domain (4th ed.; *DSM-IV;* American Psychiatric Association, 1994). As the disease progresses, memory impairment worsens and assistance is needed with instrumental activities of daily living, dressing and with handling the details of toileting. During this stage AD patients may also experience significant personality changes and behavioral symptoms and may wander or get lost. Finally, in the most severe stages of AD, the individual is no longer able to speak or comprehend language and requires constant care, including supervision and assistance in the basic everyday functional abilities of eating, toileting, bathing, and transferring (Sloane et al., 2002). Although the rate of progression through these stages varies greatly in AD cases, the clinical course of the disease is generally well established (McDowell, 2001).

Currently, Alzheimer's disease affects approximately 5.1 million Americans, 4.9 million of whom are aged 65 years and over. Future projections of the prevalence of AD estimate that as many as 11-16 million older adults could have the disease by 2050 if no cure is found or if no strategy is developed to slow its progression (Alzheimer's Association, 2007). Sloane and colleagues (2002) examined how therapeutic advances may alter disease prevalence through 2050 and reported three different scenarios. First,

there could be a delay in the onset of AD. Second, there could be a reduced rate of progression. And finally, there could be both a delayed onset and reduced rate of progression. Based on their analyses, if no therapeutic advances occur, 10.2 million persons will have the disease in 2050, of which 3.8 million will have mild disease and 6.5 million will have moderate/severe disease. In the delayed onset model, it was projected that there would be 35.6% fewer cases of AD by 2050 than baseline projection, but moderate/severe disease would constitute the majority of cases. If the disease progression were slowed, they projected a slight increase (1.2%) in the number of cases, but with a higher proportion of patients in the mild stage versus moderate to severe stages. Finally, a combined model projected a reduction in the total number of cases (37.4%) where mild cases would predominate (56%; Sloane et al., 2002).

Taken together, these studies demonstrate that there is substantial heterogeneity in cognitive functioning during the course of aging. In general, some individuals maintain their cognitive functioning, some decline gradually, and some decline sharply to a clinical diagnosis of dementia. The focus of the current project is to examine factors that may play a role in determining where older adults fall on this cognitive continuum with aging.

Theoretical Foundations: Environmental Complexity and Cognitive Reserve

It has been suggested that genetics play a large role in development of age-related brain changes or disease-related pathology, and that environmental factors play a larger role in the expression of cognitive impairments (Mortimer, Borenstein, Gosche, & Snowdon, 2005). Two theoretical perspectives, environmental complexity and cognitive reserve, may provide explanations as to how environmental factors affect the expression of cognitive impairment.

Environmental Complexity and Cognitive Reserve

The concepts of environmental complexity and cognitive reserve have great salience for understanding heterogeneity in individual performance and how the following factors contribute to this heterogeneity (Stern, 2002). Although they originated from different empirical roots, the sociology of work and brain injury, respectively, together they may help to identify environmental factors that reduce age-related differences and change and explain how these same environmental factors act at the neurophysiologic level (Small et al., 2007).

Simply stated, the environmental complexity hypothesis suggests that complex environments have a positive effect on cognitive functioning, and simple environments have a negative effect on cognitive functioning. More specifically, the complexity of an environment is a function of the diversity the stimuli, the number of decisions required, the number of considerations to be taken into account in making decisions, and the ill-defined and apparently contradictory contingencies resulting from these decisions. Accordingly, complex environments are expected to reward cognitive effort, where individuals should be motivated to develop their intellectual capacities and to generalize their use to other situations. Continued exposure to relatively simple environments may have the opposite effect since the low level of environmental demand does not foster the development of or maintenance of intellectual functioning (Schooler, 1984; Small et al., 2007).

The concept of cognitive reserve has been proposed to explain the heterogeneity in clinical outcomes between individuals who have the similar neural deficits related to disease pathology or normal age-related brain changes. Two types of cognitive reserve

have been proposed by Stern (2002) to describe this variation, passive and active. The passive model of reserve suggests that neuron and synapse number or brain size provide the basis for reserve, and consequently is determined primarily by genetics but may be influenced to some degree by environmental influences. The active model of reserve is concerned more with neural processing and synaptic organization than neuroanatomical differences. Neural processing and synaptic organization are more sensitive to environmental influences; therefore it is these changes that provide the greatest potential for increasing reserve (Stern, 2002). It is likely a combination of active and passive reserve that provides the most comprehensive explanation of the cognitive variation between individuals at the neurophysiologic level.

Factors Associated with Cognitive Functioning

Age-related and pathological changes in cognitive functioning are influenced by a combination of genetic and environmental factors (Finkel & Pedersen, 2004). It is generally thought that genetic and environmental factors operate in concert to affect risk for cognitive decline and dementia, with genetic factors affecting risk for age-related or pathological changes in the neural substrate, and environmental factors affecting risk for clinical expression of these changes (Mortimer, Snowdon, & Markesbery, 2003; Stern, 2002). Although the focus of this dissertation is to examine the influence of mid- and late-life environmental factors on cognitive functioning in older age, one should be mindful of the fact that genetic factors and early-life factors, especially educational attainment (see Andel, Hughes, & Crowe, 2005 for review), are interacting with these factors to produce the cognitive outcomes observed in older age. Furthermore, the selected mid- and late-life factors under investigation are likely influenced by other late-

life factors, such as medical comorbidies, that are also being studied for their role in cognitive vitality with aging, and that adjustment for these factors is made whenever possible.

Modifiable Factors in Mid- and Late-Life under Investigation

Evidence suggests that environmental factors become increasingly more important for individual differences in cognitive ability in late-life (Finkel & Pedersen, 2004), and that environmental factors can continue to affect older adults' cognitive functioning (Schooler, 1984). Three factors that can be modified in middle and older age, but may be just as important in early-life, are lifestyle activities, social resources and diet. The following sections provide a review of the literature describing how each of these factors has been linked to age-related cognitive differences/changes and risk for dementia and serve as the background for the three studies of the dissertation.

Study I: Lifestyle Activities

Age-related differences/changes in late-life leisure activity participation and cognitive performance have been studied by a number of researchers; however, the findings are inconsistent. A positive relationship between activity participation level and cognitive functioning has been found in several studies (e.g. Bielak, Hughes, Small, Dixon, 2007; Newson & Kemps, 2005; Wilson, Barnes, & Bennett, 2003). For example, Newson and Kemps (2005) found that participation in four categories of everyday activities (household maintenance, domestic chores, social activities, and service to others) was a significant predictor of baseline level of speed, picture naming, incidental recall, and verbal fluency; and of cognitive change over six years in speed, picture naming, and incidental recall after controlling for sensory functioning. A life course

approach was taken by Wilson and colleagues (2003) to examine how participation in cognitively stimulating activities measured at ages 6, 12, 18, 40 and current age was related to function in different cognitive systems. They found that lifetime cognitive activity was related to better cognitive performance, but only for certain tasks. Finally, using a lifestyle activity questionnaire to measure frequency of engagement in cognitive, social, and physical activities, Bielak and colleagues (2007) found that higher frequency of engagement in cognitively complex activities was related to faster latency and less inconsistency on speeded tasks concurrently, but that change activity was not associated with change in speed performance. These results suggest that current activity level may influence cognitive functioning to a greater extent than change in activity participation with aging.

In contrast to these studies, a number of studies have failed to observe that engagement in leisure activities that were socially, experientially, developmentally (Aartsen, Smits, van Tilburg, Knipscheer, & Deeg, 2002), or cognitively (Salthouse, Berish, & Miles, 2002) stimulating provided any protection against cognitive decline. It should be noted that the lack of support for an association between lifestyle activities and cognitive functioning in these studies is conceivably due to methodological/statistical issues. For example, younger adults were included in the study by Salthouse and colleagues (2002) who likely exhibited less variability in cognitive performance and engagement in activities than the older adults, which may have reduced the authors' ability to detect age-related differences in cognitive performance as a function of cognitively stimulating activity participation (Small et al., 2007).

Age-related changes in lifestyle activities *and* changes in cognitive performance have been studied in order to provide clues about the temporal relationship between cognitive functioning and engagement in lifestyle activities. Hultsch and colleagues (1999) used a measure of active lifestyle that included 70 activities classified into six groups: physical activities, self-maintenance activities, social activities, hobbies and home maintenance activities, passive information processing, and novel information processing. Longitudinal examination of the influence of engagement in these activities on maintenance of cognitive functioning over time revealed that higher engagement in novel activities at baseline and over time buffered against decline in working memory, however, the possibility that cognitive decline preceded decline in engagement was suggested. Another longitudinal study examined the association between participation in activities and cognitive performance on tests of memory, cognitive speed, and crystallized intelligence and found that declines in activity participation and cognition occurred simultaneously, and that declines in cognition occurred even in a sub-sample of individuals who maintained their level of activity participation over the course of seven years (Mackinnon, Christensen, Hofer, Korten, & Jorm, 2003). Although the authors concluded that participation in lifestyle activities may not offer protection against cognitive decline because those who maintained their level of activity participation still declined, the fact that those who maintained their activity levels were those who had lower levels of activity at baseline does not preclude the possibility that older adults who are able maintain a higher level of activity participation may be able to stave off decline.

A more recent examination of whether changes in lifestyle activities lead to a change in cognitive functioning or if changes in cognitive functioning lead to a change in

lifestyle activities was conducted by Ghisletta, Bickel, and Lövdén (2006) using a bivariate dual change score model approach. This method allows for the direct assessment of the temporal order among the variables tested, and thus can determine whether changes in lifestyle activities precede or follow changes in cognitive functioning or whether changes in both variables influence changes in the other. The results of the study revealed that increased frequency of participation in media- (e.g. listen to radio, watch television) and leisure- (e.g. play games, crossword puzzles) type activities was associated with less decline in perceptual speed.

In general, there appears to be some support for a positive association between engagement in leisure activities in late-life and cognitive functioning that warrants further research. One area that has received only minimal attention in the literature is the association between lifestyle activity participation and variability in cognitive performance. In normal aging, within-person variability, or inconsistency, refers to variability associated with a person's performance on a single task measured on multiple occasions (Hultsch et al., 2002). Evidence from studies such as Hultsch and colleagues (2002) suggest that increased inconsistency with aging could be predictive of impending cognitive decline or an indicator of neurological dysfunction, and may a more sensitive measure than mean level performance. Therefore, the purpose of the first study of the dissertation is to examine the concurrent association between participation in lifestyle activities and both mean level performance and inconsistency on four reaction time tasks. A lifestyle activities questionnaire that assessed frequency of participation in activities that are cognitively, socially, and physically stimulating and range in cognitive demands is used to measure engagement in lifestyle activities. How engagement in these lifestyle

activities is related to mean level performance and inconsistency in cognitive speed; as measured by performance on simple, choice, lexical, and semantic reaction time tasks, is tested controlling for age, gender, educational attainment, and physical health. The relationships found further our knowledge regarding (1) the types of lifestyle activities that are most strongly related to neurocognitive speed, and (2) whether mean-level performance or inconsistency is more strongly related to engagement in lifestyle activities.

Study II: Social Resources

There is now a large body of evidence supporting the association between social resources and health. Both the quantity and quality of social resources have been shown by numerous studies to be associated with mortality and morbidity (see Seeman & Crimmins, 2001; Uchino, Cacioppo, & Kiecolt-Glaser, 1996 for reviews). Diseases such as heart disease (Krumholz, Butler, Miller, Vaccarino, Williams, Mendes de Leon, et al., 1998; Mookadam & Arthur, 2004) and depressive symptoms (Jang, Borenstein, Chiriboga, & Mortimer, 2005; Yaffe, Lui, Grady, Stone & Morin, 2002) have been shown to be reduced in individuals with greater social resources. The strong link between social resources and health outcomes has led to investigations of a possible relationship between social resources and cognitive functioning in older adults.

Studies of the association between social resources and cognitive functioning have found different aspects of social resources to be related to cognitive functioning. For example, Holtzman and colleagues (2004) examined the association between social network characteristics and global cognitive functioning in a sample of high-functioning older adults. They found that a larger social network at baseline was associated with

better maintenance of cognitive ability and with a reduced risk for general cognitive decline over 12 years of follow-up. In contrast, Seeman and colleagues (2001) examined the association between social ties and support and patterns of cognitive aging and found that cognitive performance was better at baseline and at the follow-up seven and a half years later for those who received more emotional support, while they did not find that the size of social network was associated with cognitive functioning. Interestingly, being unmarried and reporting greater conflict with members of the social network was also related to better cognitive performance in their study. A more powerful study of the relationship between social ties, social integration and social engagement and cognitive functioning using random effects models also found differential importance for these social relation measures in terms of cognitive functioning (Beland, Zunzunegui, Alvarado, Otero, & Del Ser, 2005). Specifically, social engagement and social integration were found to be more important for general cognitive functioning over seven years than social ties after controlling for gender, education, depressive symptoms, functional limitations, and chronic conditions. Finally, stronger perceived social support has also been found to be related to better cognitive functioning by Yeh and Lui (2003), where having a good friend to talk to was associated with better scores on the short portable mental status questionnaire.

Several issues have created challenges for the study of social resources and cognitive performance and may account for the mixed results. First, social resources are defined differently across studies. For example, social network was defined by Holtzman and colleagues (2004) as the number of relatives and family members outside the household and the number of friends and neighbors with whom one kept in touch with by

phone or visits. In comparison, Seeman and colleagues (2001) defined social network as marital status, number of close ties with children, family, and friends, and participation in religious or other groups. To measure social support, some studies have examined emotional support available (Bassuk, Glass, & Berkman, 1999; Seeman et al., 2001), while others have also used instrumental support (Seeman et al., 2001) and indices of living arrangement and loneliness (Yeh & Liu, 2003). Further, most studies have not included measures of perceived support or negative interactions, which have been shown to be associated with cognitive functioning (Seeman et al., 2001; Yeh & Liu, 2003).

The ability to find an association between social resources and cognitive performance is likely related to the types of cognitive outcomes measured. For example, few studies have examined measures of cognitive functioning that may be most susceptible to decline with age, such as attention and perceptual speed, *and* domains that may be more strongly associated with environmental factors (e.g. social resources), such as episodic memory (Kramer et al., 2004). The majority of studies examining the association between social resources and cognitive functioning have only included measures of global cognitive ability (Bassuk et al., 1999; Holtzman et al., 2004; Yeh & Liu, 2003). Seeman and colleagues (2001) did assess the higher order functions of language, verbal and nonverbal memory, abstract reasoning, and spatial ability in their study; however, they did not assess more basic cognitive abilities and neither did any of the other studies.

In summary, evidence suggests that social resources may be important for cognitive functioning similar to health outcomes; however, further research is needed that addresses the described limitations before conclusions can be drawn. The purpose of the

second study of the dissertation is to examine the association between social resources and cognitive performance while addressing these limitations. This is accomplished by including multiple measures of social resources including social network of family, social network of friends, instrumental support, emotional support, informational support, satisfaction with support, and negative interactions and by using a more comprehensive cognitive battery that has a test of general cognitive ability, and tests of basic (i.e. attention and perceptual speed) and higher order (i.e. memory) cognitive abilities. Increasing our knowledge about the association between social resources in this way is important for tailoring interventions that may alter or modify social resources in order to improve cognitive health in older age.

Study III: Dietary factors

Dietary factors are important for cognitive functioning in late-life since they function directly by maintaining one's health and indirectly by preventing other diseases that are related to cognitive impairment, such as vascular disease. Several studies have now reported that certain micro-nutrients, including Vitamins B6, B12, folate, antioxidants (Vitamins C, E and carotenes), and polyphenols are related to the risk of dementia (Commenges, Scotet, Renaud, Jacqmin-Gadda, Barberger-Gateau, & Dartigues, 2000; Dai, Borenstein, Wu, Jackson, & Larson, 2006; Engelhart, Geerlings, Ruitenber, Van Swieten, Hofman, Witteman, et al., 2002; Morris, Evans, Bienias, Tangney, Bennett, Aggarwal, et al., 2002). Low serum levels of each of these are characteristic of people with cognitive impairment (Solfrizzi, Panza, & Capurso, 2003); therefore it is of interest whether maintaining adequate levels of these vitamins either through supplementation or through diet can reduce risk for impairment. These micro-nutrients are thought to be

important for cognitive health because they play a role in processes such as oxidative stress and inflammation, which are known to play a role in both age-related and dementia-related brain changes.

Care should be taken when studying the effect of diet on cognitive impairment in late life since there is the potential for preclinical disease processes to affect dietary patterns. Few studies have prospectively examined the relationship between midlife diet and risk of late-life dementia. Laurin, Masaki, Foley, White, & Launer (2004) examined the association between midlife dietary intake of antioxidants estimated based on a food questionnaire and the incidence of late-life dementia. Overall, the authors did not find support for a protective effect of midlife antioxidant intake on dementia risk in later life. Despite this negative finding, this study highlights the need for additional studies of dietary factors in midlife and risk of late-life dementia and its subtypes, including a more basic examination of intake of whole foods.

The role of diet in cognitive impairment with aging has not been extensively studied. The fact that diet is an important part of a healthy lifestyle and has a large impact on disease profiles suggests that dietary factors deserve more attention in future research. The focus of the final study of the dissertation is to explore the association between midlife fruit and vegetable consumption and the risk for dementia using two study designs: case-control and co-twin control. These designs test whether genetic or early environmental familial factors account for any influence of midlife fruit and vegetable intake on the risk of dementia. The risk of late-life dementia was prospectively assessed using data collected in midlife, which reduces the possibility of measuring changes in diet secondary to dementia since dementia has a long latency period.

Determining whether dietary factors in midlife can modify the risk for dementia in late-life has important implications for the types of dietary recommendations made by governmental agencies and physicians to promote the cognitive health of the population.

Summary

The current dissertation examines three aspects of environment that may be predictors of cognitive performance or cognitive impairment; lifestyle activities, social resources, and fruit and vegetable intake. This is accomplished through three independent studies which attempt to build on the previous literature and aid in the understanding of whether lifestyle factors are a feasible strategy to slow down or delay age-related cognitive decline or reduce the risk for dementia. The first study of the dissertation examines the influence of lifestyle activity participation on mean-level and inconsistency in reaction time performance. The analyses determines whether activities of varying cognitive demand are differentially related to reaction time performance, and whether inconsistency in reaction time performance is a more sensitive marker of cognitive functioning than reaction time performance at the mean-level. In the second study, the relation between seven aspects of social resources and multiple domains of cognitive functioning over five years is examined. Lastly, the third study examines the role of midlife fruit and vegetable consumption in the risk for dementia in late-life. Each of these studies is carried out using the concepts of environmental complexity and cognitive reserve as the theoretical underpinnings.

Chapter Three: Study I

Does Engagement in Lifestyle Activities Affect Inconsistency in Cognitive Speed Performance in Older Adults?

Tiffany F. Hughes, Allison A. M. Bielak, Brent J. Small & Roger Dixon

ABSTRACT

The “use it or lose it” hypothesis of cognitive aging contends that engagement in stimulating activities moderates age-related differences in cognitive performance. Using data from the Victoria Longitudinal Study (n = 511), we examined whether frequency of engagement in lifestyle activities is associated with concurrent mean-level and intraindividual variability in cognitive speed performance. Multiple regression analyses revealed that higher frequency of engagement in integrative and novel information processing activity was associated with faster and less variable cognitive speed performance. Age-differences in lexical and semantic decision time performance were moderated by engagement in self-maintenance and novel information processing activities. Overall, the findings support the notion that a higher level of engagement in cognitively demanding activities is associated with better cognitive speed performance, and that there are greater differences in reaction time performance across age as a function of engagement in self-maintenance and novel lifestyle activities.

INTRODUCTION

The potential for older adults to assume an active role in their cognitive health has recently been the focus of public health initiatives (Centers for Disease Control and Prevention and the Alzheimer's Association, 2007). Several actions have been proposed as potential strategies to maintain or improve the cognitive performance of older adults including engagement in activities that are physically, socially, and cognitively stimulating. The "use it or lose it" paradigm suggests that cognitive abilities are maintained through stimulation of the cognitive system, while age-related declines are attributable to "disuse" of cognitive abilities (see Small, Hughes, Hultsch, & Dixon, 2007). However, the current literature describing the association between engagement in activities and cognitive functioning is inconclusive, where some studies show a positive association and others do not support an association.

The concepts of environmental complexity and cognitive reserve propose psychological and physiological mechanisms to explain how engagement in lifestyle factors may affect the level of cognitive functioning in older adults and the rate of cognitive change with aging. The environmental complexity hypothesis suggests that exposure to complex environments rewards cognitive effort such that individuals will be motivated to develop their intellectual capacities and to generalize their use to other situations, whereas continued exposure to relatively simple environments will not foster the development of or maintenance of intellectual functioning (Schooler, 1984). This cognitive effort is then translated at the neurophysiologic level to more efficient neural processing and synaptic organization as described by the active model of cognitive reserve (Stern, 2002). Cognitive reserve is believed to be amenable to change

throughout the life course and to modify the trajectory of decline associated with aging such that those individuals with higher reserve will experience a slower rate of age-related cognitive change compared to those with lower reserve.

Several observational studies have been conducted in the field of cognitive aging that examine the relation between lifestyle activities and cognitive performance. For example, Newson and Kemps (2005) found that participation in household maintenance, domestic chores, social activities, and service to others was a significant predictor of current cognitive performance in speed of processing, picture naming, incidental recall, and verbal fluency after controlling for sensory functioning. Similarly, Hultsch, Hertzog, Small, and Dixon (1999) also found that higher engagement in intellectual activities buffered against decline in working memory, however, the possibility that cognitive decline preceded decline in engagement was suggested. To clarify this issue, Ghisletta, Bickel, and Lövdén (2006) used the bivariate dual change score model approach and found that increased frequency of participation in media- (e.g. listen to radio, watch television) and leisure- (e.g. play games, crossword puzzles) type activities was associated with less decline in perceptual speed, whereas the reverse association was not found.

In contrast to these studies, others have failed to observe that engagement in leisure activities buffers against cognitive dysfunction with aging. Aartsen Smits, van Tilburg, Knipscheer, and Deeg (2002) found that socially, experientially, and developmentally stimulating activities did not provide any protection against decline in general cognitive ability, immediate recall and learning, and fluid intelligence. Similarly, Mackinnon, Christensen, Hofer, Korten, and Jorm (2003) found that declines in activity

participation and cognition occurred simultaneously, and that declines in cognition occurred even in a sub-sample of individuals who maintained their level of activity participation over the course of seven years. Finally, Salthouse, Berish, and Miles (2002) found that engagement in 22 cognitively demanding activities did not buffer against age-related differences on four cognitive composite measures reflecting fluid intelligence, episodic memory, and crystallized intelligence.

The mixed findings in the literature are likely due to different methodological and analytical considerations (see Ghisletta et al., 2006; Salthouse, 2006; Small, et al., 2007 for reviews). One consideration is that detecting an association between engagement in lifestyle activities and cognitive performance requires a measure sensitive to the integrity of the central nervous system (e.g. synaptic connections). Intraindividual variability, or inconsistency, in cognitive performance refers to variability associated with a person's performance on a single task measured on multiple occasions (Hultsch & MacDonald, 2004). Increased inconsistency has been shown to be associated with older adults compared to younger adults (e.g., Hultsch, MacDonald, & Dixon, 2002; Nesselroade & Salthouse, 2004; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005), poorer overall cognitive performance (Hultsch & MacDonald, 2004; Li, Aggen, Nesselroade, & Baltes, 2001), and conditions known to affect neurological functioning (e.g. dementia, Parkinson's disease, MCI, traumatic brain injury; Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Christensen, Dear, Anstey, Parslow, Sachdev, & Jorm, 2005; Dixon, Garrett, Lentz, MacDonald, Strauss, & Hultsch, 2007; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2006; Stuss, Pogue, Buckle, & Bondar, 1994; Walker, Ayre, Perry, Wesnes, McKeith, Tovee, et al., 2000). Therefore, examining inconsistency in cognitive speed,

in addition to mean-level performance, may increase the ability to detect an association between engagement in activities and cognition since slower and more variable reaction time performance with increased age could be attributed to lower frequency of engagement in stimulating activities.

The purpose of the current study is to examine whether age-related slowing, measured by mean level and inconsistency in reaction time tasks, is related to engagement in lifestyle activities using data from the Victoria Longitudinal Study (VLS). We hypothesized that 1) increasing age would be associated with decreased participation in lifestyle activities and slower mean-level and greater inconsistency in reaction time performance, 2) higher frequency of participation in activities, particularly those that are more cognitively engaging, will be associated with faster mean-level cognitive speed and with less inconsistency in cognitive speed performance, and 3) age-related differences in reaction time performance between individuals will vary as a function of the level of engagement in lifestyle activities.

METHODS

Participants

Participants were drawn from the Victoria Longitudinal Study (VLS). The VLS is a longitudinal-sequential research project in which participants are retested every three years on an extensive battery of cognitive, physical, sensory, health, and psychological tests with new samples added every six years. A more detailed description of the VLS design, procedures, and measures can be found elsewhere (Dixon & de Frias, 2004; Hultsch, Hertzog, Dixon, & Small, 1998). The present study is based on cross-sectional

data from Wave 1 of Sample 3 that consisted of 577 community-dwelling older adults aged 55-90 years.

Measures

Cognitive Speed Variables

The measurement of cognitive speed is based on reaction time (RT) latencies in milliseconds from four multi-trial computer-based RT tasks. These four tasks require rapid responses to simple nonverbal stimuli and complex language-based stimuli, and require participants to make a decision about the stimulus by pressing a key on the response console.

Simple Reaction Time. In the simple reaction time task, the participants were presented with a warning stimulus (***) followed by a signal stimulus (+) in the middle of the screen. They were instructed to press a key as quickly as possible in response to the signal stimulus. The latency scores of fifty trials after completion of 10 practice trials served as the outcome measure.

Choice Reaction Time. In the choice reaction time task, a warning stimulus (++) was presented on the left and right of the screen followed by one changing to a square. The participants were instructed to the press key corresponding to square location as quickly as possible. Following 10 practice trials, a total of 50 trials were administered and the latency was used as the outcome measure.

Lexical Decision. The objective of the lexical decision task was for the participants to judge as rapidly as possible whether a set of 5-7 letters presented was a real English word (e.g. *island* vs. *nabion*). The time to respond by pressing one of two keys across 60 trials (30 words and 30 nonwords) served as the outcome measure.

Semantic Decision. The semantic decision task required the participants to judge as rapidly as possible whether a sentence presented was plausible (e.g. *The tree fell to the ground with a loud crash* vs. *The pig gave birth to a litter of kittens this morning.;* Palmer, MacLeod, Hunt, and Davidson (1985)). Time to press one of two keys was recorded across 50 trials (25 plausible and 25 implausible sentences) and used as the outcome measure.

Following the recommendations of previous research (Hultsch et al., 2002); we defined the lower bound for legitimate responses as 150 ms for simple reaction time, 150 ms for choice reaction time, 400 ms for lexical decision, and 1,000 ms for semantic decision. The upper bound limit was determined by calculating the mean and standard deviation for each task and occasion of measurement and removing any trials that exceed the mean by three or more standard deviations. Any latency scores falling above or below these bounds were dropped from the analyses since extremely fast or slow responses most likely represent various sources of measurement error (e.g., accidental key press, distraction of participant).

We imputed missing value estimates using a regression substitution procedure that assesses the correlations among response time across all trials (Hultsch, MacDonald, Hunter, Levy-Bencheton, &Strauss, 2000). This method of eliminating outlying trials and imputing estimates for the missing values decreases within-subject variation such that the data represent a conservative approach to examining intraindividual variability in response time performance. Following data preparation procedures, the level of cognitive speed was computed in the traditional manner as the mean RT of each individual's latency for each task. Our measure of inconsistency was computed as the

across-trial within-person individual standard deviation (ISD) about each individual's mean RT.

Activity Lifestyle

The VLS Activity Lifestyle Questionnaire (VLS-ALQ) is a validated, 70-item self-report questionnaire designed to measure frequency of participation in activities during the past two years. Frequency of participation is rated on a 9-point scale (*never, less than once a year, about once a year, 2 or 3 times a year, about once a month, 2 or 3 times a month, about once a week, 2 or 3 times a week, daily*), and scaled such that higher scores are associated with greater frequency of activity. For the present study, we classified 66 items into a 7-category classification based upon the previous validation work of Hultsch, Hammer, and Small (1993) and Hultsch and colleagues (1999). The seven subscales were defined as: (1) physical activity, such as gardening or jogging (n = 4); (2) self-maintenance, such as preparing a meal or shopping (n = 6); (3) social, such as attending church or eating out (n = 7); (4) travel, such as traveling within Canada (n = 3); (5) passive information processing, such as watching a sporting event or listening to the radio (n = 8); (6) integrative information processing, such as driving a car or playing a musical instrument (n = 13); and (7) novel information processing, such as learning a new language or preparing income tax forms (n = 25). Items within each of the seven categories were summed to form composite activity measures.

Health Composite

At each wave of measurement, the VLS Personal Data Sheet was administered and included questions pertaining to health beliefs, health conditions, and health risk factors. These questions were designed to represent four of five measures of physical

health identified by Liang (1986): chronic illness, number of illness episodes, instrumental health, and subjective health. A measure of self-reported physical health was created by summing the average scores of 34 items assessing the presence and severity of chronic illnesses in the past two years, six items assessing the number of illness episodes in the last four weeks and three items assessing the number of illness episodes in the past year, eight items assessing the extent to which health affected their daily activity patterns (i.e. instrumental health), and two items assessing how the participants rated their health in comparison to perfect health and to others their age (see Hultsch et al., 1993 and Hultsch et al., 1999 for a detailed description of the health measures). Higher scores on the composite health measures were representative of worse health.

Data Analysis

Descriptive characteristics of the sample according to age group (young-old = 53-64 years; old-old = 65-74 years; oldest-old = 75-90 years) were calculated and comparisons were made using analysis of variance between age groups. Correlation analyses were performed to examine the univariate associations among the demographic characteristics, health, frequency of activity engagement and reaction time performance. Regression analyses were conducted for each reaction time task to examine the main effects of each lifestyle activities controlling for the effects of age, gender, education, health, and the other activity measures. Interaction effects were then tested to examine whether the association between age and reaction time performance depended upon the level of engagement in lifestyle activities. Each interaction term was computed by centering the scores of the main effects to avoid multicollinearity (Aiken & West, 1991),

and was added separately to the main effect model in order to maintain a sufficient ratio between the number of subjects and predictor variables entered in the regression model. Significant interaction effects were interpreted by stratifying the select activity domains into tertiles (low, medium, and high) and examining the whether the point estimates of each activity tertile fell within the 95% confidence interval of the other two groups.

RESULTS

Sample Characteristics

Following list-wise deletion procedures, a total of 511 participants were eligible for the present analyses. Characteristics of the sample by age group are presented in Table 1.1. Compared to the young-old, the old-old and oldest-old were less likely to be women, and the oldest-old were less likely to have completed as many years of education. For engagement in lifestyle activities, the old-old were more likely to engage in passive activities and less likely to engage in physical activities compared to the young-old participants. The oldest-old were less likely to engage in travel, physical and integrative information processing activities compared to the young-old, and they were also less likely to engage in travel and integrative information processing activities in comparison to the old-old. There were also differences between each of the age groups in the frequency of self-maintenance and novel information processing activities where engagement in these activities decreased with increasing age group membership. In terms of cognitive speed performance, the oldest-old were slower and more variable on all reaction time tasks compared to both the young-old and old-old. The old-old were also slower and more variable on the choice IM and ISD and the lexical IM tasks compared to the young-old participants.

Correlations

Prior to regression analyses, we examined univariate correlations between the demographic characteristics and health and the lifestyle activity and reaction time measures (Table 2.1). Increasing age was correlated with less frequency of engagement in travel, self-maintenance, physical, integrative information processing, and novel information processing activities, and with slower reaction times and greater variability on all measures. Men tended to engage in fewer social and self-maintenance activities, and to engage more frequently in travel, integrative and novel activities. They also performed faster on choice reaction time. Reporting a lower level of educational attainment was related to less frequent engagement in travel, physical, integrative and novel activities as well as with slower mean level reaction time on all tasks, and more variability in lexical and semantic decision time. Finally, those in poorer health were less likely to engage in passive, travel, physical, integrative, or novel activities, and were slower and more variable on the semantic decision time task.

Table 3.1 shows the correlations between the activity measures and reaction time performance. More frequent engagement in travel activities was associated with faster performance on all tasks and with less variability on choice and lexical decision time. A higher level of self-maintenance activities was associated with faster and less variable choice reaction time performance. Higher level of physical activity engagement was related to faster and less variable simple, choice and lexical decision time performance as well as faster semantic decision time. More frequent engagement in integrative information processing activities was associated with faster and less variable performance

on the simple and choice reaction time measures, while engagement in novel activities was associated with faster and less variable performance on all tasks.

Regression Analyses

The results of the multiple regression analyses are summarized in Table 4.1. After controlling for age, gender, education and health, social, self-maintenance, integrative and novel activities were associated with reaction time performance. Specifically, more frequent engagement in social activities was related to slower choice reaction time, and more frequent engagement in self-maintenance activities was associated with more variable lexical decision time performance. Conversely, more frequent engagement in integrative information processing activities was associated with faster simple and choice reaction time and with slower lexical and more variable lexical and semantic decision time performance. More frequent engagement in novel activities was associated with faster and less variable performance on lexical and semantic decision time tasks.

Significant interactions between self-maintenance and novel activity engagement and age were found for performance on the lexical and semantic decision tasks (Table 5.1). Slowing of performance on each of the lexical and semantic time tasks with increasing age varied as a function of the level of engagement in self-maintenance activities such that more frequent engagement was generally associated with greater slowing as age increased. The opposite was found for novel activity participation such that more frequent engagement was generally associated with a less slowing on the lexical and semantic time tasks as age increased.

DISCUSSION

In this study we were interested in whether engagement in lifestyle activities is associated with mean-level and variability in cognitive speed performance. In addition, we sought to determine if age-related differences in cognitive speed performance were moderated by the level of engagement in these activities. This study contributes to the findings of previous research by including a measure of inconsistency in performance, which may account for some of the mixed findings in the literature testing the association between lifestyle activities and cognitive performance.

The findings of the study support the idea that a higher level of engagement in integrative and novel information processing activities is associated with faster and less variable performance on select reaction time measures. In addition, greater differences in reaction time performance were found with increasing age depending on the level of engagement in self-maintenance and novel information processing activity participation, suggesting that age differences in cognitive speed performance are influenced by the level of engagement in lifestyle activities.

Our pattern of results suggests that engagement in novel information processing activities is most strongly and consistently associated with cognitive speed performance, especially for the language-based reaction time tasks. The novel activity category included activities such as reading, doing crossword puzzles, and learning a new language. In comparison to the other activity categories, these types of activities can be considered more cognitively demanding as they primarily stimulate cognitive domains. Thus, novel activities likely provided the most direct benefits to the neurological system, possibly by strengthening or creating new synaptic connections (Stern, 2002). Additional

associations were found between more frequent engagement in integrative information processing and faster simple and choice reaction time performance. These types of activities also place demands on the cognitive system, although potentially less so than novel activities, which may be why they were associated with more basic reaction time measures. We suspect that the finding that more frequent engagement in integrative information processing activities was associated with slower lexical and more variable lexical and semantic decision time performance is attributed to collinearity between activity measures since the univariate correlations were in the expected direction. Finally, the fact that higher engagement in social and self-maintenance activities was found to be associated with slower choice reaction time and more variable lexical decision time, respectively, may be that these types of activities provide relatively little cognitive stimulation or that higher engagement in these activities may limit engagement in more cognitively stimulating activities.

The presence of interactions between age and engagement in self-maintenance and novel lifestyle activities suggests that there are differences in cognitive speed with increasing age in relation to activity participation. According to Salthouse (2006), age by activity interactions must be found to validate the *differential-preservation* hypothesis whereby "the degree to which [cognitive] performance is preserved across increasing age is postulated to differ according to the level of mental activity" (Salthouse, 2006, pg. 70). Our findings support the differential-preservation hypothesis for self-maintenance and novel activity engagement. The extent to which age-related slowing occurred for the lexical and semantic decision time tasks differed between the low, medium and high activity groups where high self-maintenance and low novel activity engagement were

associated with greater slowing and variability with increasing age. Explanations for these effects are similar to the previous discussion of the main effect findings for self-maintenance and novel activity engagement.

The fact that we did not observe additional significant interactions between age and activities may be related to the match between the type of activities the participants engaged in and the cognitive domain tested. Evidence from cognitive training intervention studies, including the Seattle Longitudinal Aging Study and the Advance Cognitive Training for the Independent and Vital Elderly (ACTIVE), suggest that cognitive training improves cognitive performance on the specific abilities trained (Ball, Berch, Helmers, Jobe, Leveck, Marsiske, et al., 2002; Schaie, 2005). For example, it would be expected that higher engagement in activities that require verbal skills, such as crossword puzzles, would be associated with better performance on a cognitive task primarily assessing verbal ability and not a task assessing memory. Furthermore, recent evidence also suggests that crystallized abilities may be better maintained throughout the life course for those whose are more engaged in stimulating leisure activities compared to those who are not (see Kramer, Bherer, Colcombe, Dong, and Greenough, 2004 for review). Since few of the activities assessed in the current study were closely associated with processing speed abilities, and only two of the reaction time tasks required some verbal skill, stronger affects between lifestyle activities and inconsistency in cognitive speed performance may have been found if higher order cognitive tasks, such as verbal ability or semantic memory, had been tested.

We expected that engagement in activities would be more strongly associated with inconsistency in reaction time performance than with mean-level performance given

the sensitivity of inconsistency to the integrity of the nervous system. Although engagement in novel activities was associated with less variability in lexical and semantic decision time, overall we found more significant relations between activity and reaction time performance at the mean-level compared to inconsistency. This finding suggests that engagement in lifestyle activities affects the neurological system at the macro level, which is better captured by measuring mean-level cognitive performance. Alternatively, observing few associations between activity engagement and inconsistency may be related to the notion that only those individuals below a certain cognitive level, or whose neurological integrity has been compromised below a certain level, would demonstrate more variable performance in relation to lower frequency of engagement in lifestyle activities (Salthouse, 2006).

Limitations of the study should be addressed. This study is a cross-sectional examination of the association between activities and cognitive performance. A fundamental issue plaguing the study of this association is whether activity decline precedes cognitive decline or the reverse (Schooler & Malutu, 2001). This question can only be addressed with longitudinal data and sophisticated statistical techniques that permit lead-lag relationships to be estimated. Furthermore, determining whether the *differential-preservation* hypothesis or the *preserved-differentiation* hypothesis, which proposes that those who are more engaged in older adulthood are likely to have been more engaged throughout life and that prior engagement essentially determines the level of cognitive performance rather than rate of change in cognitive performance, better describes the relationship between engagement in lifestyle activities and cognitive performance requires longitudinal data over the entire life course (Salthouse, 2006).

Although these types of analyses were beyond the scope of the present study, we feel that examining the concurrent relationship between frequency of activity engagement and inconsistency in cognitive speed provides new insight into how measures of processing speed ranging in cognitive effort are affected by engagement in lifestyle activities and whether inconsistency is a more sensitive marker of the benefits of engaging in lifestyle activities than is mean-level performance.

Another limitation is the representativeness of the sample. Members of VLS have a relatively higher level education, are in relatively better health, and are higher functioning than the general population (Dixon & de Frias, 2004; Hultsch et al., 1993, 1999). Since the benefits of activities on cognition may be greatest for those whose educational attainment or cognitive abilities are lower than average (e.g. Arbuckle, Maag, Pushkar, & Chaikelson, 1998; Christensen & Mackinnon, 1993; Gold, Andres, Etezadi, Arbuckle, Schwartzman, & Chaikelson, 1995), our results may have been attenuated because of the intact nature of our sample. However, previous comparisons of the cross-sectional association between self-reported health, activity, and cognitive measures in a representative sample of 1,278 community-dwelling older adults aged 65-100 (Ball, 1998) versus a select VLS sample revealed similar results, suggesting that our findings may not be biased due to the intact nature of the sample (Hultsch et al., 1999). Nevertheless, our results should be interpreted with this possibility in mind.

In conclusion, the results of this study suggest that engaging in activities that are more cognitively complex may benefit concurrent mean-level performance on reaction time tasks, especially those that are more cognitively demanding. We also found that engagement in self-maintenance and novel activities moderated age-related differences in

cognitive speed performance. Future studies should be conducted to examine longitudinal relationships between lifestyle activities and inconsistency in higher order cognitive abilities that appear to be more receptive to environmental stimulation. Until research confirms or refutes the validity of the "use it or lose it" hypothesis with respect to cognitive aging, adults of all ages should continue to engage in activities that are mentally, socially, and physically stimulating if for no other reason than to improve their quality of life.

Table 1.1 Descriptive Characteristics of the Study Variables by Age Group

	Age Group						
	53-64 years (n = 205)		65-74 years (n = 172)		75-90 years (n = 134)		
Variable	Mean	SD	Mean	SD	Mean	SD	*p -value
Age	59.63	2.95	69.37	2.96	79.90	3.57	
Gender (% Female)	77.56		59.88		61.94		<.001
Education	15.73	2.78	15.11	2.92	14.63	2.99	.003
Health	6.97	5.04	6.59	3.40	7.11	3.99	0.54
Social activity	3.20	0.95	3.15	0.92	3.10	1.01	0.64
Passive activity	3.95	0.96	4.19	0.91	4.13	1.11	0.04
Travel activity	2.18	0.80	2.19	0.76	1.90	0.90	0.003
Self-maintenance	5.17	0.93	4.92	0.98	4.62	1.03	<.001
Physical activity	4.17	1.19	3.93	1.38	3.63	1.21	<.001
Integrative information	1.54	0.72	1.51	0.70	1.29	0.63	0.003
Novel information	3.23	0.64	3.01	0.62	2.80	0.69	<.001
Simple RT - IM	312.52	71.03	316.71	69.28	361.09	78.05	<.001
Simple RT - ISD	78.02	56.45	85.87	48.68	102.92	80.52	0.001
Choice RT - IM	772.20	122.17	844.88	131.94	951.19	154.40	<.001
Choice RT - ISD	164.45	49.41	180.17	53.14	200.51	81.25	<.001
Lexical RT - IM	992.09	316.88	1092.49	462.70	1240.71	421.59	<.001
Lexical RT - ISD	294.70	197.60	338.56	231.89	408.50	276.13	<.001
Semanitc RT - IM	3268.49	1085.56	3513.76	1176.19	4050.50	1462.40	<.001
Semantic RT - ISD	1017.46	673.31	1039.45	471.91	1240.41	653.29	0.002

*ANOVA

Table 2.1 Correlations of Demographic Characteristics and Health with Lifestyle Activities and Reaction Time Performance

Variable	Age	Gender	Education	Health
Social activity	-.0.06	-0.17***	0.08	-0.02*
Passive activity	0.07	-0.01	0.04	-0.14**
Travel activity	-0.13**	0.10*	0.18***	-0.12**
Self-maintenance	-0.22***	-0.28***	-0.04***	0.004
Physical activity	-0.22***	0.05	0.09*	-0.19***
Integrative information	-0.13**	0.10*	0.20***	-0.12**
Novel information	-0.28***	0.11*	0.39***	-0.15***
Simple RT - IM	0.24***	-0.01	-0.12**	0.04
Simple RT - ISD	0.14**	-0.07	-0.07	0.04
Choice RT - IM	0.51***	-0.09*	-0.13**	0.06
Choice RT - ISD	0.27***	-0.03	-0.07	0.06
Lexical RT - IM	0.28***	-0.02	-0.18***	0.07
Lexical RT - ISD	0.21***	-0.06	-0.23***	0.08
Semanitc RT - IM	0.27***	-0.07	-0.19***	0.11**
Semantic RT - ISD	0.17***	-0.02	-0.15***	0.09*

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

Table 3.1 Correlations Between Lifestyle Activities and Reaction Time Performance

	Simple RT		Choice RT		Lexical RT		Semantic RT	
Variable	IM	ISD	IM	ISD	IM	ISD	IM	ISD
Social activity	0.001	-0.01	0.01	0.01	-0.01	-0.03	-0.03	-0.004
Passive activity	-0.03	-0.03	-0.004	-0.02	-0.04	-0.02	-0.03	-0.02
Travel activity	-0.09*	-0.08	-0.11**	-0.10*	-0.12**	-0.13**	-0.10*	-0.07
Self-maintenance	-0.06	-0.03	-0.11*	-0.12**	-0.02	-0.08	-0.02	-0.01
Physical activity	-0.14**	-0.11*	-0.20***	-0.17***	-0.12**	-0.10*	-0.09*	-0.06
Integrative information	-0.17***	-0.12**	-0.21***	-0.11*	-0.03	0.01	-0.02	0.02
Novel information	-0.17***	-0.10**	-0.26***	-0.13**	-0.29***	-0.30***	-0.26***	-0.19***

Note: IM = Intraindividual Mean; ISD = Intraindividual Standard Deviation.
* $p < .05$. ** $p < .01$. ***$p < .001$.

Table 4.1 Regression Estimates for the Association between Lifestyle Activities and Cognitive Speed

	Simple RT		Choice RT		Lexical RT		Semantic RT	
Variable	IM	ISD	IM	ISD	IM	ISD	IM	ISD
Main Effects								
Age	1.66***	0.85*	8.43***	1.68***	9.81***	3.84**	29.53***	9.25**
Gender	2.06	-9.33	-41.21**	-6.76	3.29	-0.53	292.53*	2.08
Education	-1.27	-0.15	1.33	-0.06	-9.13	-9.23*	-42.81*	-18.17
Health	-0.19	0.08	0.37	0.28	1.92	1.51	22.83	9.12
Social activity	0.98	0.26	2.07*	0.71	4.18	0.23	9.84	2.53
Passive activity	-0.29	-0.12	-0.31	-0.09	-0.33	1.03	1.27	0.67
Travel activity	-0.81	-0.92	-0.39	-1.12	-3.95	-3.10	-9.26	-2.05
Self-maintenance	-0.01	-0.05	-0.43	-0.75	1.91	4.45*	11.38	1.03
Physical activity	-0.72	-0.55	-1.38	-1.02	-3.12	-1.91	-3.69	-0.83
Integrative information	-1.00*	-0.51	-1.85**	-0.29	4.52*	4.28***	12.7	8.44*
Novel information	-0.25	-0.05	-0.83	-0.07	-6.10***	-3.97***	-16.65***	-5.95**
Model R^2	0.07***	0.02*	0.30***	0.08***	0.13***	0.14***	0.13***	0.05***
Interaction Effects								
Age*Social	-0.02	0.003	-0.04	-0.01	-0.40	-0.29	-0.93	-0.81
Age*Passive	0.02	0.02	0.02	0.04	0.23	0.10	0.45	-0.09
Age*Travel	-0.21	-0.05	-0.26	-0.14	-0.86	-0.73	-4.21	-1.69
Age*Self-Main.	0.03	0.03	0.04	-0.02	0.91**	0.60***	3.03**	1.12*
Age*Physical	-0.04	0.07	-0.18	-0.06	-0.46	-0.37	-1.69	-0.88
Age*Integrative	-0.05	-0.02	-0.06	-0.06	-0.17	-0.05	0.01	-0.22
Age*Novel	-0.05*	-0.03	-0.07	-0.01	-0.30**	-0.17**	-0.93**	-0.38*

Note: IM = Intraindividual Mean; ISD = Intraindividual Standard Deviation.
* $p < 0.05$; ** $p < 0.01$; *** $p < .001$

Table 5.1 Regression Estimates and 95% Confidence Intervals for the Association between Age and Select Cognitive Speed Measures by Activity Engagement

	Self-Maintenance			Novel Information Processing		
Variables	Low	Medium	High	Low	Medium	High
Age with						
Lexical RT - IM	5.27 (-3.12,13.66)	7.77 (2.13,13.42)	17.36 (9.62,25.10)	14.63 (4.86,24.40)	4.51 (-1.58,10.61)	7.20 (1.97,-12.43)
Lexical RT - ISD	0.77 (-3.21,4.76)	2.83 (-0.66,6.33)	8.73 (3.48,13.98)	5.77 (0.50,11.05)	2.37 (-1.36,6.10)	1.82 (-1.22,4.87)
Semantic RT - IM	15.46 (-8.07,39.00)	18.39 (-0.56,37.33)	55.39 (28.61,82.16)	43.09 (16.02,70.14)	12.35 (-6.94,31.65)	24.69 (4.21,45.16)
SemanticRT - ISD	4.91 (-5.33,15.15)	5.39 (-5.82,16.59)	16.82 (2.48,31.16)	13.23 (0.45-26.01)	2.65 (-6.40,11.70)	7.05 (-5.57,19.66)

Note: IM = Intraindividual Mean; ISD = Intraindividual Standard Deviation.

Chapter Four: Study II

The Association between Social Resources and Cognitive Change in Older Adults: Evidence from the Charlotte County Healthy Aging Study

Tiffany F. Hughes, Ross Andel & Brent J. Small

School of Aging Studies, University of South Florida

Amy R. Borenstein & James A. Mortimer

Department of Epidemiology and Biostatistics, University of South Florida

ABSTRACT

We examined associations between multiple aspects of social resources and 5-year change in performance on different domains of cognitive function. Results indicated that lower satisfaction with support was associated with decline in episodic memory performance over 5 years. We also found significant interactions between age and social networks of family and friends and satisfaction with support for the separate cognitive domains. The results suggest that social resources may be differentially important for cognitive change but that different cognitive domains respond in a similar pattern to social resources.

INTRODUCTION

Evidence that an active and socially integrated lifestyle may slow cognitive decline in old age (Bassuk, Glass, & Berkman, 1999) or reduce risk for dementia (Fratiglioni, Paillard-Borg, & Winblad, 2004) suggests that the social environment could confer protection against cognitive decline (Schooler & Malatu, 2001). However, few studies have simultaneously examined the effects of different aspects of social resources (e.g., size of social network, receipt of support, or satisfaction with social support) on the cognitive health of older adults or whether separate cognitive domains respond differently to social resources.

There is considerable variability in the manner in which social resources have been operationalized and they domains of cognitive functioning that have been measured. For example, size of social network has been the most frequently studied aspect of social resources in relation to cognitive performance (Bassuk et al., 1999; Holtzman, Rebok, Saczynski, Kouzis, Wilcox, & Eaton, 2004; Seeman, Lusignolo, Albert, & Berkman, 2001). However, other aspects of the social environment, such as emotional support, negative interactions, and satisfaction with support, have received less empirical attention despite suggestions that they may be important predictors of cognitive function (Bassuk et al., 1999; Holtzman et al., 2004; Seeman et al., 2001; Yeh & Liu, 2003).

Cognitive outcomes examined in previous studies have also been varied. The majority of studies have either used a measure of global cognitive function such as the Mini-Mental State Examination (Bassuk et al., 1999; Holtzman et al., 2004) or created a summary score of overall cognitive ability (Barnes, Mendes de Leon, Wilson, Bienias, & Evans, 2004; Seeman et al., 2001). However, different domains of cognitive functioning

have different developmental trajectories across the life span and also respond differently to environmental factors (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). Therefore, examination of how social resources influence multiple cognitive domains requires further research.

The purpose of the current study was to examine the associations between different aspects of social resources and change in multiple domains of cognition. We examined whether changes in general cognitive ability, speed and attention, and episodic memory are differentially influenced by social network of family and friends; emotional, informational, and instrumental received support; satisfaction with support received; and negative social interactions. We also examined whether the strength of the associations between social resources and change in cognitive performance vary as a function of age.

METHODS

Participants

Participants were members of the Charlotte County Healthy Aging Study, a community-based, longitudinal study of aging in which participants were initially enrolled in 1997/1998. Interested readers can find a detailed description of the sampling procedure and response rates elsewhere (Borenstein, Mortimer, Wu, Jureidini-Webb, Fallin, & Small, 2006; Small, Graves, McEvoy, Crawford, Mullan, & Mortimer, 2000). After we excluded 38 individuals who scored less than 82 on the Modified Mini-Mental State Examination (Teng & Chui, 1987), the baseline sample comprised 417 individuals. At the follow-up approximately 5 years later (M = 4.94 years, range = 4.6–5.3 years), 43 participants (10.3%) had died, an additional 36 (8.7%) had withdrawn after the baseline phase, 39 (9.4%) refused to participate, and 60 (14.4%) were unable to be contacted. This

resulted in 239 participants. Because of missing data on some predictors at baseline, the longitudinal sample consisted of 217 persons.

Measures

Cognitive Measures. The neuropsychological test battery included the Modified Mini-Mental State Examination (Teng & Chui, 1987) to measure general cognitive ability, the Stroop Test (Stroop, 1935) to measure attention, the Trailmaking Test (Parts A and B) to measure perceptual speed (Reitan & Wolfson, 1985), and the Hopkins Verbal Learning Tests (Brandt, 1991; Benedict, Schretlen, Goninger, & Brandt, 1998) comprising tests of delayed free recall, cued recall, and recognition to measure episodic memory. Based upon significant intercorrelations, we created two composite scores: speed and attention (Trailmaking, Parts A and B; and Stroop Test) and episodic memory (delayed, cued, and recognition).

Social Resources. The participants were asked 26 questions with regard to social resources at baseline. These items were derived from Lubben's (1988) Social Network Scale and social support measures from the work of Krause and Borawski-Clark (1995). Principal components factor analysis with varimax rotation was used to reduce the number of variables in the models. The principal components factor analysis revealed seven factors: *social network of family* (number of contacts with family per month, frequency of contact per month with closest relative, and number of close relatives), *social network of friends* (number of close friends, number of friends in contact at least once per month, and frequency of contact with closest friend), *emotional support* (frequency in the past month of others providing support in difficult times, providing comfort, listening or talking about private feelings, and showing interest or concern),

instrumental support (how often in the past month others provided transportation, help with housework, chores, or yard work, and help with shopping), *informational support* (frequency in the past month of others suggesting some action to take to solve a problem, making a difficult situation easier to understand, helping understand why something was not done well, and sharing what they did in a similar stressful situation), *satisfaction with support* (frequency of having someone to talk with about an important decision, and frequency of satisfaction with emotional support, instrumental support, and informational support), and *negative social interactions* (how often in the past month others placed demands, were critical, pried into affairs, and took advantage). The factors accounted for 63% of the variance.

Covariates. Demographic variables included age (in years), gender (men = 0, women = 1), education (in years), marital status (not married = 0, married = 1), and residency in Charlotte County, Florida (in years). We included a between-subjects variable to account for follow-up attrition status (yes = 0, no = 1). Personality was assessed with the NEO Five-Factor Inventory (Costa & McCrae, 1992), which measures the domains of neuroticism, extraversion, openness, agreeableness, and conscientiousness.

Analyses

We used Proc MIXED in SAS Version 9 (Littell, Milliken, Stroup, & Wolfinger, 1996) to examine whether each social resource factor contributed unique variance in cognitive performance above and beyond the other factors. For each cognitive outcome, we simultaneously entered all of the baseline social resource factors and interactions between each social resource factor and continuous age while adjusting for baseline age,

gender, education, marital status, residency status, and personality in the model. For the analysis of cognitive change, we also modeled the influence of years of follow-up time. In order to interpret significant interactions, we stratified age into young-old versus old-old based on a median split (age 73/74), recentered age, and examined whether the point estimates of each group fell within the 95% confidence interval (CI) of the opposite group.

RESULTS

Descriptive Analyses

At baseline, the study participants' mean age was 72.4 years (*SD* = 6.2); they had an average of 14.0 years (*SD* = 2.7) of education; 51.8% were women; 77.5% were married; and they had lived an average of 12.6 years (*SD* = 8.5) in Charlotte County, Florida. The independent samples *t*-tests comparing the follow-up sample (*n* = 217) to those who were not followed (*n* = 200) revealed that those followed were younger and more likely to be married, had lower neuroticism scores, had higher scores on extraversion and conscientiousness, had lived fewer years in Charlotte County, and received less instrumental support at baseline. They also performed better on the measures of speed and attention and episodic memory at baseline compared to those who were not followed ($p < .05$ for all analyses).

Random Effects Models

As shown in Table 1.2, examination of the fixed effects of social resources on baseline levels of cognitive performance revealed that more negative social interactions and greater satisfaction with support were associated with better general cognitive ability. Better performance on speed and attention was also associated with greater satisfaction

with support. Over the 5 years, less satisfaction with support was marginally associated with decline in episodic memory performance.

Tests of modification by age yielded significant findings for both baseline and change in cognitive performance (see Table 1.2). Stratifying the sample into young-old versus old-old based on a median split (age 73/74) revealed differences between the young-old (estimate = 0.20, 95% CI = 0.05, 0.34) and old-old (estimate = –0.35, 95% CI = –0.60, –0.11) for change in general cognitive ability as a function of social network of friends and between the young-old (estimate = 3.55, 95% CI = 1.40, 5.69) and old-old (estimate = –3.61, 95% CI = –7.92, 0.70) for change in speed and attention as a function of social network of friends. No other interactions satisfied the criteria for statistical significance.

DISCUSSION

In this study, we examined whether social resource measures were differentially important for cognitive change with aging. The pattern of associations found between the different social resource factors and cognitive change across multiple domains adds support for the notion that social resource factors may be important to the cognitive health of older adults. However, the results also indicate that separate cognitive domains respond similarly to social resources, as we saw parallel patterns of associations across cognitive domains.

Of the social resource factors, baseline satisfaction with support and social network were most consistently related to cognitive performance. Consistent with Yeh and Liu (2003), who found stronger perceived positive support from friends to be related to better cognitive function, we found that greater satisfaction with support was

associated with better general cognitive performance and speed and attention, as well as less decline in episodic memory performance, and that these relations were modified by age.

The relation between having a smaller social network and cognitive decline as a function of age is consistent with a number of previous studies (Barnes et al., 2004; Bassuk et al., 1999; Beland, Zunzunegui, Alvarado, Otero, & Del Ser, 2005; Holtzman et al., 2004). These findings are also in line with the conceptual model proposed by Berkman, Glass, Brissette, and Seeman (2000), whereby social networks provide the opportunity for social support and engagement and therefore have a broader influence on the social environment than other aspects of social resources.

Previous studies have reported that receipt of emotional social support is associated with cognitive performance (Bassuk et al., 1999; Seeman et al., 2001). At the main effect level, we did not find that receiving less emotional, instrumental, or informational support was related to poorer cognitive performance. However, we did find that age modified the relation between baseline episodic memory performance and emotional support. Because our sample was a relatively healthy sample of older adults, we did not expect that receipt of more instrumental or informational support would be associated with less cognitive decline over time, as this would likely have been an indication of poorer health status, including cognitive health. Similar to Seeman et al. (2001), we also found that reporting more negative social interactions was associated with better general cognitive ability. This finding may be the result of negative social interactions providing a greater level of stimulation, which benefits cognitive functioning.

The ability to find associations between social resources and cognitive performance is likely related to the types of cognitive outcomes measured. One strength of the current study was the measurement of multiple aspects of cognitive function—including general cognitive ability, speed and attention (basic cognitive abilities), and episodic memory (complex cognition)—in order to explore the associations between various types of social resources and change in separate cognitive domains. We found that the cognitive domains responded similarly to social resources. In contrast to Gerstorf, Herlitz, and Smith (2006), we found that the main effect of gender was associated with change in episodic memory (estimate = 0.82, $p = .0001$) after we controlled for education and attrition.

Although the results of the current study are informative, we should acknowledge several limitations. First, participants from the Charlotte County Healthy Aging Study are Caucasian, well educated, and in relatively good health, which may limit the generalizability of the results; in addition, there was a considerable amount of attrition in the sample. Second, there was relatively high stability in cognitive function over time, which may have reduced our ability to detect associations. Third, we did not correct for multiple comparisons. However, given the paucity of previous research examining multiple aspects of social resources, we view these results as a starting point for future research. Finally, we were unable to fully explore the directionality of the association (i.e., whether a lower level of social resources leads to poor cognitive function, or whether poor cognitive function leads to a lower level of social resources).

In conclusion, our results suggest that the social environment may be important for the cognitive health of older adults. These findings are especially important in that

social resources are amenable to change. Future studies need to (a) examine the determinants of social resources in older adults (e.g., socioeconomic status, geographic proximity to family, or number of children) in order to identify persons at risk for cognitive decline, (b) examine the influence of health and level of social engagement in these associations, and (c) include three or more waves of data to assess the reciprocal relations between social resources and cognitive change with aging.

Table 1.2 Models predicting cognitive performance as a function of social resources[a]

	Global Cognition		Speed and Attention		Memory	
	Estimate	***p***	**Estimate**	***p***	**Estimate**	***p***
Fixed Effects - Intercept						
NegInt	0.42	**0.03**	-2.09	0.48	-0.18	0.48
Satisfaction	0.45	**0.02**	7.43	**0.01**	0.29	0.22
Emotional	-0.08	0.64	1.07	0.69	0.05	0.82
Informational	0.06	0.76	-4.27	0.13	0.04	0.88
Instrumental	0.01	0.94	-4.71	0.09	0.18	0.45
Family	0.10	0.57	4.83	0.08	0.40	0.09
Friends	0.13	0.49	3.74	0.17	-0.09	0.70
NegInt x Age	0.01	-0.61	0.47	0.28	-0.01	0.71
Satisfaction x Age	0.04	0.12	1.04	**0.01**	0.12	**0.001**
Emotional x Age	0.03	0.30	0.56	0.21	0.09	**0.02**
Informational x Age	-0.01	0.73	-0.57	0.18	0.01	0.76
Instrumental x Age	-0.02	0.47	-0.49	0.29	0.001	0.98
Family x Age	-0.06	**0.05**	0.10	0.83	0.06	0.11
Friends x Age	-0.06	**0.05**	-0.36	0.40	-0.04	0.31
Fixed Effects - Time						
NegInt	0.09	0.25	0.11	0.93	-0.05	0.63
Satisfaction	0.09	0.22	1.24	0.30	0.18	0.06
Emotional	-0.05	0.45	0.07	0.95	-0.02	0.83
Informational	0.004	0.95	0.87	0.45	0.01	0.93
Instrumental	-0.01	0.88	-0.004	0.99	0.08	0.36
Family	0.09	0.17	0.53	0.62	0.01	0.92
Friends	-0.05	0.50	0.54	0.64	0.06	0.51
NegInt x Age	0.003	0.74	-0.04	0.84	0.01	0.34
Satisfaction x Age	0.02	0.07	0.24	0.18	0.03	**0.04**
Emotional x Age	0.01	0.37	0.12	0.51	0.02	0.18
Informational x Age	0.01	0.32	0.21	0.23	0.004	0.78
Instrumental x Age	-0.01	0.43	0.14	0.47	0.01	0.44
Family x Age	-0.03	**0.03**	-0.12	0.51	0.004	0.80
Friends x Age	-0.04	**0.002**	-0.38	**0.04**	-0.01	0.35

[a]All models were adjusted for age (centered), education, gender, marital status, residency, attrition status, and personality characteristics (neuroticism, extraversion, openess, agreeableness, conscientiousness).
Note: NegInt = Negative social interactions

Chapter 5: Study III

Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins

T. F. Hughes, BS, R. Andel, PhD, B. J. Small, PhD, A. R. Borenstein, PhD, J. A. Mortimer, PhD, A. Wolk, DMSc, B. Johansson, PhD, L. Fratiglioni, MD, PhD, N. L. Pedersen, PhD, and M. Gatz, PhD

ABSTRACT

Objective: To examine the association between fruit and vegetable consumption in midlife and the risk for all types of dementia and Alzheimer's disease (AD).

Methods: Participants were 3,306 members of the population-based Swedish Twin Registry who completed a diet questionnaire approximately 30 years prior to cognitive screening and full clinical evaluation for dementia as part of the HARMONY study. A total of 300 twins were diagnosed with dementia. Eighty-one complete twin pairs discordant for dementia (50 discordant for AD) were identified from among the participants. Data were analyzed with case-control and co-twin control designs.

Results: In the case-control analyses**,** medium or great consumption of fruits and vegetables, compared to no or small, was associated with decreased risk of all types of dementia (OR 0.73, 95% CI 0.53-1.00) and AD (OR 0.59, 95% CI 0.42-0.85) after adjustment for demographic characteristics and lifestyle variables. Effect-modification was observed, with a stronger inverse association between fruit and vegetable consumption and AD risk for women (vs. men), those who consumed one or more drinks per week (vs. none), and those who reported angina in midlife (vs. those who did not). Results from the co-twin analyses were uninformative because twin pairs were rarely dissimilar in their extent of fruit and vegetable consumption.

Conclusion: A diet with medium or great consumption of fruits and vegetables in midlife may protect against dementia and AD later in life, especially when some other risk factors are present.

INTRODUCTION

Nongenetic risk factors are thought to play an important role in the etiology and expression of dementia and may be the focus of interventions to reduce disease risk (Andel, Hughes, & Crowe, 2005). Several epidemiologic studies suggest that fruit and vegetable intake may be related to dementia (Commenges et al., 2000; Dai et al., 2006; Engelhart et al., 2002; Morris et al., 2002). Given the long preclinical phase of dementia (Bäckman, Jones, Berger, Laukka, & Small, 2005; Elias, Beiser, Wolf, Au, White, & D'Agostino, 2000) and evidence that difficulties performing instrumental activities of daily living (Barberger-Gateau, Fabrigoule, Helmer, Roach, & Dartigues, 1999) and weight loss (Stewart, Masaki, Xue, Peila, Petrovitch, White, et al., 2005) occur during this phase, the relation between diet and dementia can be misinterpreted in the absence of a sufficient time lag between dietary assessment and dementia onset. Further, the observed associations found between diet and dementia may also be accounted for by genetic or early life influences since dementia is highly heritable (Gatz et al., 2006) and dietary habits in adulthood may be influenced by genetics (Heitmann, Harris, Lissner, & Pedersen, 1999; Rankinen & Bouchard, 2006) or by childhood and adolescent behaviors (Mikkila, Rasanen, Raitakari, Pietinen, & Viikari, 2005). However, these relationships remain largely unexplored.

We examined the relation between the relative intake of fruits and vegetables at midlife and the risk of dementia approximately three decades later in members of a large population-based twin study. Using case-control analyses, we tested whether a medium or great proportion of fruits and vegetables in the diet offered protection against dementia and AD compared to no or small proportion. To test whether unmeasured genetic or

familial factors could account for observed relations using a case-control design, we analyzed the same data using a co-twin control design.

METHODS

Participants

The Swedish Twin Registry (STR) is the largest twin registry in the world and consists of three population-based cohorts of like-sexed twin pairs. It was initially designed to study the relative importance of genes and environment on several diseases (Lichtenstein, De Faire, Floderus, Svartengren, Svedberg, & Pedersen, 2002). This study draws from the members of the cohort born between 1886 and 1925 who responded to a questionnaire mailed in 1967.

In 1998, the HARMONY study was initiated to examine the relative influences of environmental and genetic factors on the etiology of AD and other dementias, to identify genes that increase the risk for dementia, and to identify specific environmental risk or protective factors for dementia and AD. Members of HARMONY consisted of all twins who were at least 65 years of age at time of assessment in HARMONY (Gatz, Fratiglioni, Johansson, Berg, Mortimer, Reynolds, et al., 2005). The HARMONY study was reviewed and approved by the institutional review board of the University of Southern California and the regional ethics board at the Karolinska Institute.

In all, 5,692 twins eligible for the HARMONY study had data for fruit and vegetable intake from 1967. Dementia status was available for 3,778 of these twins, based on two-stage case ascertainment consisting of cognitive screening followed by clinical diagnostic evaluation. Among the others, 1,020 refused to participate, 255 were not reachable, 283 were unable to be interviewed and an informant was not available, 104

died before they could be screened, and 252 were screened but not seen for a clinical evaluation either by design (because their co-twin was long deceased and the pair would be uninformative) or due to refusal. After excluding those with incomplete covariate data, 3006 control participants and 300 participants diagnosed with dementia (199 with AD) were used for the case-control analyses (58.1% of those eligible). For the co-twin analyses, we identified 81 twin pairs discordant for dementia (18 of whom were discordant for proportion of fruits and vegetables in diet), and 50 pairs discordant for AD (12 of whom were discordant for proportion of fruits and vegetables in diet).

Measures

Dementia Diagnosis. Individuals were screened and clinically evaluated for dementia as part of the HARMONY study. A random sample of HARMONY members was selected each month for the primary telephone screening phase to identify twins positive for cognitive dysfunction and possible dementia (Gatz, Reynolds, John, Johansson, Mortimer, Pedersen, 2002). Those who screened positive for cognitive dysfunction and their co-twin, even if they screened negative, were contacted for a follow-up clinical evaluation of dementia status according to the DSM-IV diagnostic criteria (details of the study design, including dropout analyses can be found elsewhere).

Dietary Assessment. Included in the STR 1967 questionnaire regarding lifestyle factors were 23 items pertaining to dietary habits. Fruit and vegetable consumption was assessed by a single item on a 4-point relative scale with response choices being "great part", "medium part", "small part", or "no part". For the current study, the "no" and "small" part categories and the "medium" and "great" part categories were collapsed due

to the small number of participants reporting that fruits and vegetables made up "no part" or "great part" of their diet.

Covariates. The demographic characteristics of age at follow-up (continuous), sex (male/female), and education were included as covariates. Education was measured as basic versus more than basic. In the first part of the 20th century in Sweden, a basic education consisting of 6 years or, later, 7 years of school was mandatory. Participants described their education as the highest level attained, that is, basic education, gymnasium, vocational high school, or university.

In addition, baseline (1967) values reported for current smoking status (yes/no), alcohol consumption (no drinks per week/one or more drinks per week), exercise (hardly any or light/regular or hard), body mass index (BMI=weight[kg] over height squared [m^2]; measured as BMI <25 and BMI ≥25), self-reported angina pectoris (yes/no), and total food intake in comparison to others (less or as much/more or much more) were regarded as potentially confounding variables. Unmeasured genetic and familial factors were controlled by design in the co-twin control design.

Statistical Analyses

The data were analyzed using two study designs: case-control and co-twin control. The case-control analyses compare cases to unrelated controls to evaluate the risk for disease given a particular exposure. The co-twin design uses disease-discordant twin pairs by comparing the diagnosed twin to the non-demented co-twin.

The characteristics of the participants by diagnostic status and by level of fruit and vegetable consumption were compared using independent samples *t*-tests for continuous variables and χ^2 test for categorical variables. In the case-control analysis, we

examined the risk for dementia in relation to the relative consumption of fruit and vegetables using unconditional logistic regression to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). To further reduce the possibility that participants had signs of preclinical dementia at the time of the dietary assessment, in a secondary analysis we restricted the sample to those who were 60 years of age or younger in 1967. We also examined effect-modification by age group in 1967 (<51 years, 51-61 years, >61 years), sex, education, smoking, alcohol, BMI, self-reported angina, total food consumption compared to others, and exercise by estimating multiplicative interaction terms in fully adjusted logistic regression models for dementia and AD. All confidence intervals were adjusted to account for data dependence due to the inclusion of complete twin pairs (Moradi, Hans-Olov, Ekrom, Wendren, Floderus, & Lichtenstein, 2002).

Similar analyses were conducted for the co-twin control study using conditional logistic regression to estimate ORs and 95% CIs based on within-pair comparisons. Within each twin pair, the twin who reported greater consumption of fruits and vegetables was assigned a value of 1 and the co-twin was assigned a value of 0. When twins reported the same intake level, both twins were assigned a value of 0 and did not contribute to the calculation of the point estimate. Crude and adjusted ORs were calculated. For adjusted models, mean values were imputed for smoking status, alcohol consumption, exercise, angina pectoris, and total food intake in comparison to others in order to retain the maximum number of twin pairs in the analyses. Less than 10% of the data were missing on each imputed covariate. All analyses were conducted using SAS version 9 (SAS Institute, 2003) with *p*-values less than 0.05 (two-tailed) interpreted as being significant.

RESULTS

Case-Control Analysis

Comparisons between the 3,306 participants and the 1914 drop-outs showed that the drop-outs were on average 0.92 years older (t= 8.27, $p < 0.001$), more likely to be female (70% of the drop-outs versus 62% of the participants, $\chi^2 = 32.56$, $p < 0.001$), less likely to attain more than basic level of education (25% of the drop-outs versus 36% of the participants, $\chi^2 = 60.48$, $p < 0.001$), and less likely to consume one or more drinks of alcohol weekly (61% of the drop-outs versus 69% of the participants, $\chi^2 = 39.21$, $p < 0.001$). The drop-outs did not differ from the participants in terms of current smoking status, angina pectoris, BMI, exercise, total food intake in comparison to others, or consumption of fruits and vegetables in 1967 ($p > 0.05$).

The characteristics of the cases and controls are shown in Table 1.3 for dementia and AD status. Compared to controls, cases were older at baseline and at cognitive screening, were more likely to be female and to have completed less than basic education, were less likely at midlife to report being a current smoker, to drink alcohol, or to consume some or much more food compared to others. AD cases also were also more likely to report that fruits and vegetables made up no or small part of their diet.

Table 2.3 presents the characteristics of the sample by relative consumption of fruits and vegetables at midlife. A larger number of participants reported that fruits and vegetables made up a medium or great proportion of their diet compared to no or small part. Women reported a greater consumption of fruits and vegetables compared with men, as did those with more than a basic education, non-smokers, those without self-reported angina and those who engaged in hardly any or light physical exercise.

The association between fruit and vegetable consumption at midlife and dementia or AD is shown in Table 3.3. Compared with those reporting no or small proportion of fruits and vegetables, those whose diet consisted of a medium or great part of fruits and vegetables had a reduced odds of dementia and AD after adjusting for age, sex, education, current smoking status, alcohol consumption, exercise, BMI, self-reported angina, and total food consumption in comparison to others. The risk of dementia was reduced by 27% (95% CI 0.53-1.00), and the AD risk was reduced by 41% (95% CI 0.42-0.85) in the fully adjusted models. Results of the analyses restricted to those less than 60 years of age (n = 2929 controls; n = 269 dementia cases; n = 175 AD cases) in 1967 were not substantially different. A medium or great part compared to no or small part still appeared to offer protection against dementia (OR 0.70, 95% CI 0.51-0.96) and AD (OR 0.57, 95% CI 0.39-0.83) in the fully adjusted models.

We examined whether the association between fruit and vegetable consumption and risk of AD was modified by demographic and lifestyle variables by estimating multiplicative interaction terms. The analyses revealed that sex, alcohol drinking and the presence of self-reported angina in midlife modified the association between fruits and vegetables and risk of AD (Table 4.3). The inverse association between fruit and vegetable consumption and AD risk was stronger for women, those who consumed at least one or more drinks per week, and those who reported having angina in midlife. Including all cases of dementia did not substantially change the results.

Co-Twin Analysis

Results of the co-twin control analyses are displayed in Table 5.3. None of the odds ratios approached statistical significance. Notably, only 22% of the pairs who were discordant for dementia were also discordant for fruit and vegetable consumption.

DISCUSSION

Using dietary assessments collected about three decades prior to dementia evaluation as part of a large population-based study of twins, we found in case-control analyses that the consumption of fruits and vegetables in midlife may contribute to protection against dementia and AD in later life.

Fruits and vegetables contain a number of compounds with antioxidant properties (e.g. vitamins C and E, carotenoids, and polyphenols). Previous epidemiologic studies have reported that higher intake of antioxidant compounds from dietary sources such as fruits and vegetables are associated with a reduced risk of dementia (Commenges et al., 2000; Dai et al., 2006; Engelhart et al., 2002; Morris et al., 2002). It has been proposed that these compounds offer neuroprotection by scavenging free radicals whose accumulation in the brain may contribute to the pathogenesis of dementia (Behl, 1999). Fruits and vegetables also contain Vitamin B, which may be important for AD prevention since Vitamin B_{12} deficiency also has been reported to increase the risk of AD (Wang, Wahlin, Basun, Fastborn, Winblad, & Fratiglioni, 2001).

The protective effect of higher fruit and vegetable intake in our study was modified by sex, drinking alcohol and having self-reported angina pectoris in midlife. These findings suggest that those who are at higher risk for AD, specifically women (Andersen, Launer, Dewey, Letenneur, Ott, Copeland, et al., 1999) and those with

vascular risk factors (Luchsinger, Reitz, Honig, Tang, Shea, & Mayeux, 2005; Rosendorff, Beeri, & Silverman, 2007) may also benefit more from fruits and vegetables in their diet in midlife. Certain types of alcohol, mainly wine, contain flavonoids that offer protection against dementia (Truelsen, Thudium, & Grenbaek, 2002). Despite a link between excess alcohol consumption and vitamin B1 (thiamine) deficiency and Wernicke–Korsakoff Syndrome (Thomson & Marshall, 2006), moderate alcohol consumption of any type has been shown to reduce the risk of dementia (Mukamal, Kuller, Fitzpatrick, Longstreth, Mittleman, & Siscovick, 2003; Ruitenberg, van Swieten, Witteman, Mehta, van Diujn, Hofman, et al., 2002), AD (Luchsinger, Tang, Siddiqui, Shea, & Mayeux, 2004), and the risk of vascular conditions that may also affect dementia risk (Mukamal, Chung, Jenny, Kuller, Longstreth, Mittleman, et al., 2006). Therefore, the consumption of a medium or great part of fruits and vegetables in the diet and moderate alcohol consumption may have a synergistic influence on dementia and AD risk. This possibility should be explored.

A majority of studies on the relation between fruit and vegetable intake and incident dementia have had relatively short intervals between dietary assessment and dementia diagnosis, ranging between 4 and 6 years (Commenges et al., 2000; Dai et al., 2006; Engelhart et al., 2002; Morris et al., 2002). With such a short interval, it is possible that those who were to develop dementia already had made changes to their diets at the baseline assessment. Our findings suggest that fruit and vegetable intake measured in midlife, long before signs of dementia are likely to appear, has an effect on the risk of dementia in later life. Restricting our sample to include those 60 years or younger at the

time of dietary assessment did not alter our findings, further supporting the inverse association between midlife fruit and vegetable intake and subsequent risk of dementia.

Our case-control findings differ from those of the Honolulu-Asia Aging Study (HAAS) where midlife intake of antioxidants including beta-carotene, vitamin C, and flavonoids was not significantly associated with incident dementia and its subtypes (Laurin et al., 2004). This may be related to the different methods of data collection. We used a self-report of dietary habits whereas the HAAS study examined beta-carotene, vitamin C, vitamin E, and total energy intake from food diaries/recalls or food frequency questionnaires. There may also be differences in dietary preferences between the study populations.

In contrast to the case-control results, the co-twin control results were statistically non-significant. When co-twin control results do not replicate case-control results, this pattern typically indicates that genetic and unmeasured early life influences may explain the case-control findings. Previous work from the STR and HARMONY demonstrates that dementia is strongly heritable (Gatz et al., 2006) and that food preferences reflect the influence of both genes and shared environment (Heitmann et al., 1999). Early life environment influences also affect the risk of dementia (Borenstein, Copenhaver, & Mortimer, 2006) and dietary preferences into adulthood (Mikkila et al., 2005). In the sample of twin pairs here, only 22% of the pairs who were discordant for dementia were also discordant for fruit and vegetable consumption. Taken together, the results of this study suggest that the beneficial effects of fruit and vegetable consumption may be greatest if implemented in early life when life-long dietary habits are being formed.

Limitations of this study should also be mentioned. First, variables assessed at baseline, including the intake of fruits and vegetables, were self-reported and hence susceptible to social desirability bias. However, such misreporting is unlikely to vary across cases and controls and therefore would be unlikely to bias the results. Second, diet was measured only at one time point. This does not allow the stability of the diet to be assessed. However, only 13% of controls and 12% of dementia cases (11% of AD cases) reported a past change in their diet, and adjustment for this variable did not alter our findings. Third, we were unable to adjust for total energy intake. We did adjust for self-reported total food consumption compared to others and BMI, which did not confound our findings. Finally, using prevalent cases of dementia can lead to a differential survival bias. However, if lower fruit and vegetable intake increases the risk of mortality (Genkinger, Platz, Hoffman, Comstock, & Helzlsouer, 2004), then our results would likely underestimate the association with dementia. Future studies might examine patterns of food intake at midlife with incident dementia cases.

Table 1.3 Characteristics of the Participants in the Case-Control Study by Disease Status

	Controls	Dementia cases	*p*-value	Alzheimer's Disease cases	*p*-value*
n	3,006	300		199	
Age at baseline, Mean (SD)	47.67 (4.74)	52.50 (5.68)	<.001	52.63 (5.64)	<.001
Age at cognitive screening , Mean (SD)	79.16 (4.70)	83.93 (5.57)	<.001	84.09 (5.57)	<.001
Follow-up years, Mean (SD)	31.48 (0.91)	31.43 (0.96)	0.33	31.46 (0.95)	0.69
Sex, % Female	59.45	73.67	<.001	77.39	<.001
Education , % more than basic	38.72	22.33	<.001	23.62	<.001
Smoke, % Yes	30.27	21.33	<.001	20.60	0.04
Drink alcohol, % Yes	71.49	56.33	<.001	56.78	<.001
Body mass index , % ≥25	8.08	9.67	0.34	7.54	0.78
Angina pectoris, % Yes	25.35	24.00	0.61	23.12	0.48
Total food intake compared to others,					
% some or much more	9.61	5.33	0.01	4.02	0.01
Exercise, % hardly any or light	81.87	86.00	0.07	86.43	0.10
Fruits and Vegetable Consumption			0.14		0.03
% No or Small Part	20.36	24.00		26.63	
% Medium or Great Part	79.64	76.00		73.37	

*Independent samples t-test or Chi-square statistic comparing controls and cases.

Table 2.3 Characteristics of Participants in the Case-Control Study by Relative Consumption of Fruits and Vegetables at Midlife

	Relative Consumption of Fruits and Vegetables		
	No or Small Part	Medium or Great Part	*p* -value*
n	684	2622	
Age at baseline, Mean (SD)	48.19 (4.97)	48.09 (5.04)	0.62
Age at cognitive screening, Mean (SD)	79.65 (4.91)	79.57 (5.00)	0.70
Follow-up years, Mean (SD)	31.46 (0.92)	31.48 (0.91)	0.55
Sex, % Female	41.67	65.71	<.001
Education , % more than basic	28.95	39.40	<.001
Smoke, % Yes	34.94	28.03	<.001
Drink alcohol, % Yes	68.71	70.48	0.37
Body mass index , % ≥25	8.92	8.05	0.46
Angina pectoris, % Yes	29.09	24.22	0.01
Total food intake compared to others, % some or much more	10.23	8.96	0.31
Exercise, % hardly any or light	78.80	83.14	0.01

* Reflects Mentel-Haentzsel chi-square test for trend across levels of fruits and vegetables or test for trend within a linear univariate regression model.

Table 3.3 Case-Control Analyses of the Association between Midlife Fruit and Vegetable Consumption and Dementia or Alzheimer's Disease (AD)

	Relative Consumption of Fruits and Vegetables		
	No or Small Part	Medium or Great Part	*p* -value
Dementia Cases/Controls	72/612	228/2394	.
AD Cases/Controls	53/612	146/2394	.
Crude OR (95% CI)			
Dementia	1.00 (ref.)	0.81 (0.61-1.07)	0.14
AD	1.00 (ref.)	0.70 (0.51-0.97)	0.04
Adjusted OR* (95% CI)			
Dementia	1.00 (ref.)	0.72 (0.53-0.99)	0.03
AD	1.00 (ref.)	0.59 (0.41-0.85)	<0.01
Adjusted OR† (95% CI)			
Dementia	1.00 (ref.)	0.73 (0.53-1.00)	0.04
AD	1.00 (ref.)	0.59 (0.42-0.85)	<0.01

Note. OR = odds ratio; 95% CI = 95% confidence interval; ref. = reference group.

* models adjusted for age at cognitive screening (continuous), sex (men/women), and education (basic/more than basic).

† models adjusted for variables mentioned above and smoking (yes/no), alcohol drinking (yes/no), body mass index (<25/≥25), total food compared to others (less or more/some more or much more), angina pectoris (yes/no), and exercise (hardly any or light/regular or hard).

Table 4.3 Stratified Analyses for Fruit and Vegetable Consumption and Risk of Alzheimer's Disease

	Relative Consumption of Fruits and Vegetables	
	No or Small Part	Medium or Great Part
	OR	OR (95% CI)
Stratum		
Sex		
Male (Cases/Controls)	14/375	31/844
	1.00 (Ref)	1.08 (0.55-2.09)
Female (Cases/Controls)	39/237	115/1550
	1.00 (Ref)	0.46 (0.31-0.70)
p for interaction	<.001	
Alcohol		
Yes (Cases/Controls)	32/424	81/1725
	1.00 (Ref)	0.53 (0.33-0.85)
No (Cases/Controls)	21/188	65/669
	1.00 (Ref)	0.75 (0.43-1.31)
p for interaction	<.001	
Self-reported angina pectoris		
Yes (Cases/Controls)	18/175	28/587
	1.00 (Ref)	0.32 (0.16-0.63)
No (Cases/Controls)	35/437	118/1807
	1.00 (Ref)	0.74 (0.49-1.39)
p for interaction	0.001	

*Models adjusted for age at cognitive screening (continuous), sex (men/women), education (basic/more than basic), smoking (yes/no), and alcohol drinking (yes/no), body mass index (<25/≥25), total food consumption compared to others (less or more/some more or much more), angina pectoris (yes/no), and exercise (hardly any or light/regular or hard).

Table 5.3 Co-Twin Control Analyses of the Association between Midlife Fruit and Vegetable Consumption and Risk of Dementia and Alzheimer's Disease

	Total pairs	Cases higher/Co-twin higher	OR (95% CI)	*p*- value
Dementia	81	10/8		
AD	50	7/5		
Crude OR (95% CI)				
Dementia			1.25 (0.49-3.17)	0.64
AD			1.40 (0.44-4.41)	0.57
Adjusted OR* (95% CI)				
Dementia			1.25 (0.49-3.20)	0.64
AD			1.40 (0.44-4.43)	0.56
Adjusted OR† (95% CI)				
Dementia			1.32 (0.48-3.62)	0.59
AD			1.53 (0.40-5.94)	0.54

Note. OR = odds ratio; 95% CI = 95% confidence interval; ref. = reference group.

* models adjusted for education (basic/more than basic).

† models additionally adjusted for smoking (yes/no), alcohol drinking (yes/no), body mass index (<25/≥25), total food compared to others (less or more/some more or much more), angina pectoris (yes/no), and exercise (hardly any or light/regular or hard).

Chapter Six: Concluding Remarks

With the growing number of older adults, the identification and implementation of strategies to maintain cognitive health with aging has profound implications for future nursing home usage, healthcare costs, caregiver burden, personal and societal resources, as well as quality of life in general (Andel et al., 2005). Although the idea that older adults can play a role in their cognitive health is intuitively appealing, evidence from previous studies is equivocal. In an attempt to contribute to the state of knowledge of how environmental factors influence cognitive functioning with aging, the purpose of this dissertation was to conduct three studies to determine whether lifestyle activities, social resources, and fruit and vegetable consumption may potentially be useful strategies to maintain cognitive functioning or reduce the risk of dementia with aging. The findings of the three studies will be summarized in the following section.

The first study examined the influence of engagement in lifestyle activities on age-related differences in cognitive speed performance in a sample of participants from the Victoria Longitudinal Study. The findings supported the notion that higher engagement in integrative and novel information processing activities is related to faster and less variable cognitive speed performance on select reaction time tasks. The results also suggested that the level of engagement in activities moderated age-related differences in cognitive speed performance. These results of this study are consistent with previous studies where more cognitively demanding activities are related to cognitive performance, and that age-related differences in cognitive performance are

modified by engagement in certain types of lifestyle activities in old age. Overwhelming support for the idea that engagement in activities would be more closely associated with inconsistency in cognitive performance compared to mean-level was not found, but may be attributed to the fact that the VLS sample is a select sample whose cognitive level, or neurological integrity, was not compromised enough to detect stronger associations.

Data from the Charlotte County Healthy Aging Study were used to examine the association between social resources and cognitive change over five years in Study II. In general, the results suggest that lower satisfaction with social support that is received from others is associated with decline in episodic memory performance over five years. Significant interactions between age and social networks of family and friends and satisfaction with support were also found for the separate cognitive domains such that these resources become more important with increasing age to maintain general cognitive ability, as well as speed and attention abilities. The results suggest that social resources may be differentially important for cognitive change, but that different cognitive domains respond in a similar pattern to social resources.

The final study of the dissertation examined whether midlife consumption of fruits and vegetables was associated with the risk of dementia and Alzheimer's disease in members of the Swedish Twin Registry and HARMONY studies. A reduced risk of all types of dementia and AD was found for those who consumed a medium or great proportion of fruits and vegetables in their diet compared to no or small proportion in the entire sample (case-control analysis). This reduced risk was greater for females compared to males, those who consumed alcohol at least once a week compared to abstainers, and for those who self-reported angina in midlife. No significant associations

were found when the sample was reduced to only complete twin pairs in the co-twin control analysis. However, because few twin pairs were found to be discordant for both dementia and the amount of fruits and vegetables in their diet in midlife, these findings may be considered uninformative. The protective effect of fruits and vegetables in the case-control study is consistent with the majority of previous studies (Commenges et al., 2000; Dai et al., 2006; Engelhart et al., 2002; Morris et al., 2002). The possibility remains that genetic and early life influences account for these findings.

Collectively, these studies suggest that environmental factors can potentially influence cognitive functioning in later life. The first study added new insight into how engagement in lifestyle activities is associated with inconsistency in cognitive performance in addition to mean-level performance. This is important given that inconsistency has been shown to be a sensitive marker of the health of the central nervous system (Hultsch et al., 2002). The second study shed light on whether different types of social resources are differentially associated with cognitive performance. The majority of previous studies had focused on social networks, but research also suggested that other types of social resources may be important for cognitive functioning. Understanding the relative importance of different types of social resources can help target future research. The final study drew upon existing data on fruit and vegetable consumption collected approximately 30 years before dementia assessment. The findings of this study are less likely to be biased by the preclinical dementia phase compared to previous studies because of the extended time period between diet and dementia assessments, and thus the interpretation that greater consumption of fruits and vegetables is protective against dementia is likely to be more valid.

LIMITATIONS

Although each of the studies provided new insight into the relation between environmental factors and cognitive health, their limitations should also be acknowledged. First, Study I was a cross-sectional examination of the association between lifestyle activities and cognitive speed performance. This type of analysis limits our ability to conclude whether engagement in activities is associated with cognitive change and to further determine the directionality of the association (i.e. does decline in activities proceed decline in cognition or vice versa). Longitudinal data with two or more follow-up waves and the use of latent difference score or dual change score modeling should be carried out in future studies. Second, the VLS sample can also be considered a select sample of older adults who are relatively highly educated, in good health, and whose activity level and cognitive performance are above average. Finally, our findings may have been attenuated since the activities assessed did not train speed of processing abilities and prior research has shown there to be little transfer of benefits outside the cognitive domain that is trained. Future studies should examine the association between these activities and inconsistency in higher order cognitive tasks (e.g. memory, verbal abilities).

Limitations of Study II include the fact that the CCHAS sample can also be considered a select sample of older adults, which limits the external validity of the findings as well as limited the amount of variability in cognitive change. In addition, a number of participants were lost during the study follow-up period which may have biased the findings. Lastly, although this study examined cognitive change over time, we were not able to assess the temporal order of the associations between social resources

and cognitive functioning. Follow-up studies are needed using three or more waves of data collection in order to assess whether a lower level of social resources leads to declines in cognitive function, or whether poor cognitive function leads to fewer social resources.

The final study was limited by the measurement of fruit and vegetable consumption being based on one question that asked participants to report the proportion of fruits and vegetables in their diet on a four-point scale ranging from "no part" to "great part". This did not permit an estimate of the vitamins consumed or total energy intake, and also increased the chances of misclassification of exposure. Although the measurement of diet can be considered prospective, the cases are considered prevalent with respect to dementia diagnosis, which may have led to confounding by a survival bias or underestimation of the actual effect. Future studies should be conducted looking at dietary patterns since interactions among foods likely affect dementia risk. In addition, incident dementia cases should be studied in order to determine whether dietary factors affect the age of onset in twins concordant for dementia.

A general limitation across the studies that is also noteworthy is the fact that three different samples were used for each study, which does not allow for comparisons to be made with respect to the relative importance of each of the environmental factors in relation to cognitive health.

FUTURE DIRECTIONS

This dissertation research was driven by the desire to further our understanding of how modifiable risk factors are related to normal cognitive aging and the risk of dementia in late life. Ultimately, these, and other similar studies, will guide future intervention

studies designed to help older adults improve, maintain, or delay the onset of cognitive impairments associated with normal aging and dementing processes. Key questions for future studies in this arena are with respect to timing. For example, is it ever too late to change behavior, or can adults of any age benefit their cognitive health by modifying their behavior? Will the greatest benefits be seen if changes are implemented earlier rather than later in life, and how long do individuals need to engage in such behaviors to benefit their cognitive health? It is imperative that future studies investigating environmental risk factors for cognitive decline and dementia are conducted from a life course perspective in order to disentangle the temporal order of the relations between these factors and cognitive function.

Another key issue when examining the association between lifestyle variables and cognitive health with aging is the underlying mechanism of action. The current studies were limited by the data available, but future studies should examine how each of these factors is affecting cognitive reserve at the neurophysiologic level. Studies will need to include measures of brain imaging and biomarkers in order to investigate the structural and functional underpinnings of the current factors under investigation as well as other lifestyle characteristics. Findings from these studies will then increase our ability to develop more effective and specific strategies for those most vulnerable to cognitive deficits with aging. Future studies should also examine if there are intervening variables at play, such as vascular health conditions or other comorbidites, which may affect the risk of cognitive decline or dementia. The potential to improve or maintain cognitive abilities by controlling risk factors in the pathway leading to cognitive detriments could be a more feasible option since many treatments and strategies are already available.

One final direction for future studies is examining ways to identify as early as possible those most susceptible to poor cognitive health in late life who would stand to benefit most from the strategies investigated in the current dissertation. Although these factors may in and of themselves help to identify these individuals, other markers of impending cognitive decline associated with aging and dementia should also be investigated in parallel, including unmodifiable risk factors. This will allow for the implementation of strategies at the most opportune time in order to maximize their effectiveness and ultimately reduce the incidence of cognitive impairments and dementia in the future.

In conclusion, the current dissertation addressed an important public health issue that is expected to affect millions of Americans in the near future as the baby boom generation comes of age: cognitive health in late life. For most, the fear of losing cognitive abilities with aging, especially memory, is greater than physical disability. Although the results found in the three studies described here are not definitive, they lend support for the belief that individuals can play an active role in their cognitive health across the lifespan. Most importantly, the modifications suggested by the current findings pose no health risks, so adults of all ages should consider their everyday behaviors and environment as a potential way to successfully age in terms of cognition.

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APPENDICES

Appendix A: Action Letter

Dear Ms. Hughes:

Thank you for submitting a revised version of your manuscript, "The Association between Social Resources and Cognitive Change in Older Adults: Evidence from the Charlotte County Healthy Aging Study," to the Journal of Gerontology: Psychological Sciences (JG: PS). Your letter clearly describes the changes you have made in response to the Reviewers' and my comments, and I believe you have satisfactorily addressed most of our concerns. After carefully reading the revised manuscript and your detailed letter, I have decided that the manuscript is now ready for publication in JG: PS.

I will forward a copy of the manuscript to our Director of Publications, Patricia Walker, for copyediting. You will be sent a copy of the editorial changes for your approval. In addition, you will receive page proofs after the manuscript is typeset, which you should check very carefully. You will be given an opportunity to purchase reprints at that time.

Also, I have included a copy of the certification form that all authors of the manuscript must sign. Please make sure the contact information at the top of the form is correct and follow the directions on the form for returning it to us as soon as possible.

I look forward to the publication of this manuscript. I believe it will make an important contribution to the literature. Congratulations on completing this excellent research. Thank you for submitting your interesting work to JG: PS.

Sincerely yours,

Thomas M. Hess, Ph.D.
Editor
Journal of Gerontology: Psychological Sciences
Department of Psychology
North Carolina State University
Box 7801
Raleigh, NC 27695-7801
(919) 515-1729 (phone)
(919) 515-1716 (fax)
jg_psychsci@ncsu.edu

Appendix B: Curriculum Vitae

Tiffany F. Hughes

University of South Florida School of Aging Studies
4202 E. Fowler Avenue MHC 1352
Tampa, FL 33620-8100
Telephone: (813) 974-3237 Fax: (813) 974-9754
Email: thughes@health.usf.edu

Education

University of South Florida, Tampa, FL
Ph.D. in Aging Studies, 2008
Dissertation: The role of lifestyle factors in cognitive aging and dementia.
Advisors: Dr. Brent J. Small, Dr. Ross Andel

University of South Florida
M.P.H. Epidemiology, 2008
Advisor: Dr. James A. Mortimer

Allegheny College, Meadville, PA
B.S. Neuroscience and Psychology with honors, 2001

Professional Experience

Graduate Research Assistant

University of South Florida, Tampa, FL, 2005-2008
Supervisor: Dr. Brent J. Small

Johnnie B. Byrd, Sr. Alzheimer's Center & Research Institute, Tampa, FL, 2005-2008
Supervisors: Dr. Huntington Potter, Dr. Brent J. Small

Research Assistant

University of South Florida, Department of Biochemistry and Molecular Biology, Tampa, FL, 2002-2005
Supervisor: Dr. Huntington Potter

University of Pittsburgh, Department of Neurology, Pittsburgh, PA, 2001-2002
Supervisor: Dr. Paula Clemens

Internship

The Memory Disorder Clinic of Sarasota Geriatrics at Sarasota Memorial Hospital, Sarasota, FL, Summer 2005
Supervisors: Kathleen Housewart, Dr. Bruce Robinson

Mayo Alzheimer's Disease Research Center, Mayo Clinic, Jacksonville, FL, Summer 2000
Supervisors: Dr. Michelle Nicole, Dr. Michael McKinney

Teaching Experience

Instructor

University of South Florida, School of Aging Studies, Fall 2007 and Spring 2008
Course Title: Physical Changes and Aging

University of South Florida, School of Aging Studies and Department of Psychology, Summer 2006 and Summer 2007
Course Title: Psychology of Aging

Teaching Assistant

University of South Florida, School of Aging Studies, Summer 2008
Course Title: Health Promotion and Aging

University of South Florida, School of Aging Studies, Spring 2007
Course Title: Introduction to Gerontology

University of South Florida, School of Aging Studies and Department of Psychology, Fall 2006
Course Title: Psychology of Aging

Allegheny College, Fall 2000
Course Title: Health and Psychophysiology

Allegheny College, Fall 1999
Course Title: Physiological Psychology

Publications

Hughes, T.F., Andel, R., Small, B.J., Borenstein, A.R., & Mortimer, J.A. (in press). The association between social resources and cognitive change in older adults: Evidence from the Charlotte County Healthy Aging Study. *Journal of Gerontology: Psychological Sciences.*

Bielak, A.A.M., **Hughes, T.F**., Small, B.J., & Dixon, R.A. (2007). It's never too late to engage in lifestyle activities: Significant concurrent but not change relationships between lifestyle activities and both mean level and intraindividual variability in cognitive speed. *Journal of Gerontology: Psychological Sciences, 62,* P331-P339.

Small, B.J., **Hughes, T.F.**, Hultsch, D.F., & Dixon, R.A. (2007). Lifestyle activities and late-life changes in cognitive performance. In Y. Stern (ed.), *Cognitive Reserve: Theory and Applications* (pp.173-186). New York: Taylor & Francis.

Costa, D.A., Cracchiolo, J.R., Bachstetter, A.D., **Hughes, T.F.**, Bales, K.R., Paul, S.M., et al. (2007). Enrichment improves cognition in AD mice by amyloid-related and unrelated mechanisms. *Neurobiology of Aging, 28(6),* 831-844.

Andel, R., **Hughes, T.F.**, & Crowe, M.G. (2005). Strategies to reduce the risk of cognitive decline and dementia. *Aging Health, 1(1),*107-116.

Bilboa, R., Srinivasan, S., Raey, D., Goldberg, L., **Hughes, T**., Roelvink, P. W., et al. (2003). Binding of adenoviral knob to the coxsackievirus-adenovirus receptor is crucial for transduction of fetal muscle. *Human Gene Therapy, 14(17),* 645-649.

Bilboa, R., Raey, D., **Hughes, T**., Biermann, V., Volpers, C., Goldberg, L., et al. (2003). Fetal muscle gene transfer is not enhanced by an RGD capsid modification to high-capacity adenoviral vectors. *Gene Therapy, 10(21),* 1821-1829.

Manuscripts in Progress

Hughes, T.F., Andel, R., Small, B.J., Borenstein, A.R. Mortimer, J.A., Wolk, A., Johansson, B., Fratiglioni, L., Pedersen, N.L., & Gatz, G. (submitted). Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins.

Hughes, T.F., Bielak, A.A.M., Small, B.J., & Dixon, R.A. Does Engagement in Lifestyle Activities Affect Inconsistency in Cognitive Speed Performance in Older Adults?

Presentations

Hughes, T.F., Andel, R., Borenstein, A.R., Mortimer, J.A., Wolk, A., & Gatz, M. (November, 2007). Mid-life fruit and vegetable consumption and risk for dementia in Swedish twins. Poster presentation at the 60th Annual Scientific Meeting of the Gerontological Society of America, San Francisco, CA.

Small, B. J., Jacobsen, P. B., Andrykowski, M. A., **Hughes, T. F.**, Sharp Rawson, K., & Iser, L. (November, 2007). Genetic variation and cognitive performance in breast cancer survivors and non-cancer controls. Paper presented at the National Cancer Institute Small Grants Meeting, Rockville, MD.

Hughes, T.F., Small, B.J., Potter, H., Borenstein, A.R., & Mortimer, J.A. (November, 2006). Pupillary response to tropicamide is related to cognitive performance in a non-demented sample of older adults. Poster presentation at the 59th Annual Scientific Meeting of the Gerontological Society of America, Dallas, TX.

Hughes, T.F., Andel, R., Small, B.J., Borenstein, A.R., & Mortimer, J.A. (April, 2006). Social resources, health and cognitive performance in a population- based sample of older adults: The Charlotte County Healthy Aging Study. Poster presentation at The Cognitive Aging Conference, Atlanta, GA.

Hughes, T.F., Andel, R., Small, B.J., Borenstein, A.R., & Mortimer, J.A. (April, 2006). Social resources, health and cognitive performance in a population- based sample of older adults: The Charlotte County Healthy Aging Study. Poster presentation at Epidemiology of Alzheimer's Disease Scientific Research Conference, San Diego, CA.

Hughes, T.F., Bielak, A.A.M., Small, B.J., & Dixon, R.A. (November, 2005). Effects of lifestyle activities and cognitive reserve on level and variability of cognitive speed. Poster presentation at the 58th Annual Scientific Meeting of the Gerontological Society of America, Orlando, FL.

Bielak, A.A.M., **Hughes, T.F**., Small, B.J., & Dixon, R.A. (November, 2005). Does an engaged lifestyle predict cognitive level and inconsistency 3 and 6 years later? Poster presentation at the 58th Annual Scientific Meeting of the Gerontological Society of America, Orlando, FL.

Costa, D.A., Cracchiolo, J.R., Bachstetter, A.D., **Hughes, T.F**., Bales, K.R., Paul, S.M., Mervis, R.F., Arendash, G.W., Potter, H. (November, 2005). Enriched housing improves cognition in AD mice by amyloid-related and unrelated mechanisms. Poster presentation at the 35th Annual Meeting of the Society for Neuroscience, Washington, D.C.

Hughes, T.F., Bielak, A., Small, B.J., & Dixon, R.A. (April, 2005). Lifestyle activities, cognitive reserve, and intraindividual variability in cognitive functioning. *The USF College of Arts and Sciences Session of the Fourth Annual Graduate Student Research Symposium*. Tampa, FL.

Honors and Professional Activities

Member, Gerontological Society of America, 2005-present

University of South Florida Student Representative to the Gerontological Society of America, 2006-2007

President, Student Association for Aging Studies (SAAS), University of South Florida, 2006-2007

Admission to Doctoral Candidacy with Distinction, Spring 2006

Travel grant recipient, USF College of Arts and Sciences Social Sciences Session of the Fourth Annual Graduate Student Research Symposium, April 2005

School of Aging Studies Fellowship, University of South Florida, 2004-2005

Student Member, Psi Chi, 1999-2001, Treasurer, 2000-2001

ABOUT THE AUTHOR

Tiffany F. Hughes received her Bachelor's of Science degree in Neuroscience and Psychology from Allegheny College, Meadville, PA in May of 2001. She entered the Ph.D. in Aging Studies program and the University of South Florida in the Spring of 2004 with an interest in lifestyle factors that influence cognitive aging and dementia.

While in the Ph.D. program, Ms. Hughes was employed as a Graduate Research Assistant in the School of Aging Studies and at the Johnnie B. Byrd Alzheimer's Center and Research Institute where she assisted in ongoing research projects. In addition, she also was employed as a Graduate Teaching Assistant in the School of Aging Studies where she was primarily responsible for teaching the undergraduate Psychology of Aging and Physical Changes with Aging courses. Ms. Hughes first authored one peer-reviewed publication and co-authored three additional publications while enrolled as a student, as well as presented her research at multiple national conferences.