ABSTRACT

Title of Document: EXAMINING THE ROLE OF STRESSFUL LIFE EVENTS ON COGNITION AND DETERMINING MEDIATING AND MODERATING PATHWAYS AMONG POSTMENOPAUSAL WOMEN

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BACKGROUND: Major life events are an inevitable process of the life span. Preliminary evidence suggests that the stress arising from major life events may serve as a risk factor for cognitive function decline. Evidence also indicates external (e.g., physical activity) and internal factors (i.e., psychological variables) can attenuate the physiologic effects of stress.

PURPOSE: The primary aim of this dissertation was to investigate the independent and interactive effects of stressful life events on cognitive function among a sample of postmenopausal women. The possible moderating and or mediating role of external and internal factors on the relationship between stressful life events and cognitive function were also examined.

METHODS: Data from the Women's Health Initiative Memory Study were analyzed. To control for any treatment effects, only data from participants randomized into the

placebo groups were pooled and used for all analyses (n = 3775). All participants had five data collections points, baseline through four years of follow-up. Linear mixed effects models were used to answer all prospective research questions.

RESULTS: Our results appear to indicate that there was a negative relationship between stressful life events and cognitive function scores. Reporting an ill spouse/partner was associated with lower cognition scores compared to those without reporting a spouse/partner (B = -0.68, p < 0.0001). Exposure to three or more stressful life events at every data collection period was also associated with lower cognitive function scores (B = -0.61, p = 0.021). External factors did not moderate this negative relationship; however, internal factors such as optimism, hostility, and negative expressiveness appeared to mediate. Specifically, exposure to more stressful life events was associated with less favorable psychological states, which in turn, were associated with lower cognitive function scores.

CONCLUSION: Our results appear to lend support that exposure to certain life events and repeated exposure of stressful life events is associated with lower cognitive functioning. Our findings provide modest evidence that psychological mechanisms are an important pathway through which stressful life events affect cognitive functioning over time among post-menopausal women. While stressful life events are largely unavoidable, the associated increased risk of cognitive function decline may be in part offset by various psychological factors.

EXAMINING THE ROLE OF STRESSFUL LIFE EVENTS ON COGNITION AND DETERMINING MEDIATING AND MODERATING PATHWAYS AMONG POSTMENOPAUSAL WOMEN

By

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CHAPTER 1: INTRODUCTION

Stressful life events

Definition

Stress is a broad and general concept describing an organism's reactions to environmental demands (R.S. Lazarus, 1966). Psychological stress may be defined as a response to a threatening event that evokes a stress response and strains an individual's ability to handle imposed demands (R. S. Lazarus & Folkman, 1984). A stressor is any condition or event that evokes a stress response and may be categorized as physical, spiritual, emotional, social, economic, or intellectual (R. S. Lazarus & Folkman, 1984). A psychosocial stressor can be defined as "any life event or life change that may be associated temporally with the onset, occurrence, or exacerbation of a mental disorder" (American Psychiatric Association, 1994). Stressors are relative and specific to the individual. In turn, an individual's perception of a threatening event, whether real or not, is pivotal in the process whereby stress affects health (Cohen, Kamarck, & Mermelstein, 1983).

Stressors can be categorized as acute or chronic. In the simplest meaning, *acute stress* is an event, experience, or situation that happens once or is short in duration; it is the most common form of stress. In small doses, acute stress may be thrilling and exciting, but overexposure to acute stress may be exhausting and lead to psychological distress, tension headaches, upset stomach, and other symptoms (American Psychiatric Association, 2006). *Chronic stress* arises from situations or events that are longer in duration or often occurring and don't have an immediate or quick solution. The day-to-

day hassles of daily life, daily traffic jams, marital problems, financial worries, and job demands are some examples of sources of chronic stress. Chronic stress is thought to have more of a negative impact on health outcomes because of the repeated stimulation of the fight or flight reactions that can push the body's systems out of balance and cause dysregulation (McEwen, 1998).

Stressful Life Events

Major life events are considered a measure of life stressors (Rahe, 1979). Major life event stressors are characterized by potentially high-impacting events, such as parents divorce or changing schools. For the purpose of this proposal, stress arising from major life events were termed stressful life events. In general, the purpose of measuring life events is to demonstrate a temporal sequence between an increase in the number of life events and a corresponding increased risk for disease. It is hypothesized that the impact of major life events are additive whereby more events are expected to have a greater impact.

Significance of stressful life events

Psychological stress has gained acceptance as a significant public health problem, given its association with morbidity and mortality across the life course. Stressful life events are a product of life and are both relevant and u navoidable. Although stressful life events appear to be a risk factor for several chronic diseases, there is a paucity of research addressing: 1) the impact on cognitive function; and 2) mediators or moderators of the stress–psychopathology relationship, despite repeated calls for such research. Identifying mechanisms linking stressful life events to cognitive

function among older women may prove a vital step for public health professionals to develop preventive interventions that reduce the prevalence of stress-related morbidity and mortality.

Physical activity

Accumulating evidence indicates that regular physical activity can attenuate the physiologic effects of age-related decline in cognitive function. Few large prospective cohort studies that include female participants have highlighted the protective role of regular physical activity in lowering the risk of cognitive function decline. While these results provide evidence of a basis for the protective role of regular physical activity in maintaining and enhancing cognitive functioning in older adults, no study has included a diverse sample of elderly women. Further, previous studies have not controlled for an inclusive set of physical (e.g., BMI, blood pressure, comorbidities) and emotional (e.g., social support) confounders. Consequently, there seems to be a need for evidence that can detail the amount of physical activity that is warranted to produce beneficial results against cognitive function decline.

Cognitive function

Cognitive Function is the process of thought that involves aspects of perception, reasoning, thinking, and remembering. There are seven main cognitive domains: IQ, learning and memory, speed of info processing, language, orientation, abstract reasoning, and executive functioning. There are 2 major categories of long-term memory: *Declarative memory* which is the conscious and voluntary recall of previously learned information (e.g., language and verbal memory). Episodic and semantic are

two categories of declarative memory. For instance, questions such as "where were you today" and "what is the definition of…" are examples of items considered episodic and semantic respectively. *Procedural* memory is the major category type of long-term memory including motor skills and knowledge. Learning to ride a bike, learning to play a musical instrument or learning to swim are examples of procedural learning.

Prevalence

Subtle decrements in cognitive function predict future dementia and may be considered a marker of preclinical disease (Kawas et al., 2003). Dementia is a common geriatric syndrome that is marked by declines in memory and other cognitive functions that may ultimately lead to a loss of independent function (American Psychiatric Association, 2006). Alzheimer's disease is the most common form of dementia for people aged 65 and above (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). In 2000, there were ~ 4.5 million individuals with Alzheimer's disease in the US (Hebert et al., 2003). With the impending retirement of the baby-boom cohort, the prevalence of Alzheimer's disease is expected to double by 2025 and nearly triple by 2050 (Hebert et al., 2003).

Risk Factors of Cognitive Function Decline

Gender. The burden of disease is not equally distributed, as there are data to suggest women may be two to three times more likely than men to develop Alzheimer's disease (Birge, 1996). Brain volume is a hypothesized risk factor for dementia and cognitive decline in later life. However, assessment of brain volume is expensive and may not be readily applied to large samples. Measurement of the head circumference is

a more economical and more widely accessible method of estimating brain volume (Lee et al, 2009). Since women on average have smaller head circumferences than men, women are more likely to be at greater risk for cognitive function decline.

Age. For many researchers, age is considered the strongest known risk factor for Alzheimer's disease. A study using community-based sample estimated the annual incidence of Alzheimer's disease for people aged 65 to 69 years was 0.6%, and 8.4% for those 85 years and older (Hebert et al., 1995). A meta-analysis of 23 studies reported the incidence of Alzheimer's disease increased exponentially with age until 90 years (Jorm & Jolley, 1998).

Education. Cross-sectional studies have shown that education is a strong predictor of cognitive function (Anstey & Christensen, 2000). Some researchers propose that education is the most non-biological risk factor for cognitive performance on nearly all cognitive tests (Albert et al., 1995). A review of cognitive function correlates concluded that education appears to influence maintenance of mental status, memory and crystallized abilities (e.g., general knowledge, verbal fluency and vocabulary), but not fluid abilities (e.g., reasoning and induction). However, these results appeared independent on whether education was used as a categorical or continuous variable (Anstey & Christensen, 2000).

Significance of Cognitive Function

The etiology of age-related dementia, e.g., loss of brain function, is not well understood, but it is likely to be complex and multifactorial. While brain deterioration and cognitive decline are considered common characteristics of aging, not everyone

experiences decline at the same rate and/or to the same degree. These individual differences in aged persons suggest that deterioration and decay is not an inevitable product of aging. Thus, research on risk factors and protective factors for diminished cognitive function in aged adults is of critical public health importance.

Protective factors in the direct or indirect pathway

The theoretical framework on which this dissertation is based is the stress process theory. In general, the stress process theory mainly explains psychopathology of health outcomes in terms of exposure to stress and ameliorative factors, such as social support, psychological attributes, and behavioral factors. Specifically, the mental and physical health consequences of stress exposure can be attenuated by external (e.g. physical activity) and internal (e.g. psychological) variables. This theory was modified based on the variables that were available in the Women's Health Initiative database.

Internal factors

Women may rely on various internal and external resources as a way to cope with negative stressors or life events. The most prevalent internal resources used that have been studied in the literature include optimism (Carver et al., 1993; Epping-Jordan et al., 1999), hostility, expression of negative emotion (King & Emmons, 1990), and ambivalence over the expression of emotions (King & Emmons, 1990). The commonly reported indicator of external resources used to cope with negative stressors is social support (Ashing-Giwa, 1999; Cohen & Syme, 1985; Glanz & Lerman, 1992; Israel & Schurman, 1990).

Overall theoretical model

It is reasonable to extend a model toward a health outcome such as cognition, given the negative association between stress and cognition and the protective effects of internal and external resources on health outcomes. Within the context of a model of risk factors versus protective factors, we propose that stressful life events is the exposure or risk factor whereas psychosocial factors, social support, and physical activity are the protective factors. Relative to the stress-cognition relationship, we propose that internal and external resources may act as mediators and physical activity may act as a moderator. Specifically, individuals who are: more optimistic, less hostile, less ambivalent, and better at expressing negative emotions are less likely to view and react to negative life events in a manner that taxes the stress regulatory systems. Since it is less likely that stressful life events is a cause of physical activity, it is reasonable to hypothesize that physical activity is a moderating variable instead of a mediating variable. For instance, individuals who experience high amount stressful life events but are more physically active might experience less cognitive function decline, compared to those who have high amount stressful life events but are less active.

Rationale for using Women's Health Initiative data

Based on published literature regarding stressful life events and cognition, it was evident that the following methodological issues needed to be addressed in order to add to the current body of evidence: 1) a study using longitudinal data; 2) a study that operationalized stressful life events several ways in order to elucidate if single items, the sum score, or a cumulative effect has an association with cognition; and 3) a study

grounded in a theoretical construct that examined a comprehensive overview of how stressful life events may affect cognition. In other words, a study that examined the direct and indirect pathways of the association between stressful life events and cognition; and 4) a study with a large enough sample size to perform moderation and meditational analyses while controlling for a host of confounding variables.

We chose data from the Women's Health Initiative in order to address the aforementioned flaws in existing literature. Data from the Women's Health Initiative allowed for us to conduct a study that had longitudinal data with multiple data points among a large cohort of postmenopausal women. This database had variables that assessed several key factors in the direct and indirect pathway, as stipulated by the stress process theory. Further, we wanted to examine older women since it appears women in general are at higher risk for cognitive function decline.

Research Questions

The primary aim of this dissertation was to investigate the independent and interactive effects of stressful life events on cognitive function among a sample of postmenopausal women. A secondary aim is to investigate a possible moderating and mediating role of external and internal factors on the relationship between stressful life events and cognitive function. The aims of the dissertation were addressed through the following research questions:

Manuscript 1: Research questions and hypotheses
R1: What is the cross-sectional association between aggregate and individual stressful life events and cognitive function? **H1:** Stressful life events will be negatively related to cognitive function. Specifically, individuals exposed to less or no stressful life events will have higher cognitive functioning scores, compared to those with high stressful life events.
R2: What is the prospective association between aggregate and individual stressful life events and cognitive function? **H2**: Stressful life events will be positively related to cognitive function decline. Specifically, individuals exposed to less or no stressful life events will have higher cognitive functioning scores, compared to those with high stressful life events.

Manuscript 2: Research questions and hypotheses
R3: What is the prospective association between physical activity and cognitive function? **H3:** Physical activity will be positively related to cognitive function. Specifically, individuals with higher levels of physical activity will have higher cognitive functioning scores, compared to those with low levels of physical activity.
R4: Does meeting public health physical activity guidelines protect against cognitive function decline?

H4: Those who do not meet public health physical activity guidelines will have lower cognitive function scores compared to those who do meet guidelines.

Manuscript 3: Research questions and hypotheses

R5: Is the relationship between stressful life events and cognitive function influenced by external and/or internal pathways?

H5: Both behavioral and psychological factors will contribute to lower cognitive function scores. External factors (e.g., physical activity, social support) will moderate and internal factors (e.g., hostility, optimism, negative expressiveness, ambivalence) will mediate the stress-cognition relationship. Specifically, those exposed to more stressful life events will have a less favorable psychological state, and in turn, the less favorable psychological state will be associated with lower cognitive function scores.

Methods

Data from the Women's Health Initiative Memory Study (WHIMS; *n* = 7,479), a subset of participants randomly selected from the WHI Hormone Therapy Trial (WHI HT), were used to address all specific questions. The WHI is a large, multicenter investigation of postmenopausal women enrolled in one of the 3 randomized clinical trials (Hormone Therapy, Diet Modification or Calcium Vitamin D) or the Observational Study. The WHI was initiated in 1992 and enrolled participants at one of 40 WHI clinical centers nationwide. Participants were followed annually up to 8.5 years (*M* = 5.2 yrs).

The WHI HT was stopped early due to the unfavorable risk-to-benefit ratio and evidence of early harm (Writing Group for the Women's Health Initiative Investigators, 2002). The decision to stop the WHI HT also ended WHIMS.

WHIMS is a double-masked, placebo-controlled, clinical trial. Thirty-nine of the WHI clinical centers and 10 satellites participated in WHIMS. Participants in the WHIMS, an ancillary study to the WHI HT, were recruited between May 1996 and December 1999 from women in the WHI HT. A total of 7,480 women ages 65-79 were recruited from the WHI HT. Of the 7,480 women, 2,948 are in the estrogen only (E-alone) study for women without a uterus at the time they enrolled and 4,532 are in the estrogen plus progestin (E+P) study for women with a uterus at time of enrollment. Participants were followed annually up to 8 years (*M* = 4.5 yrs). To control for the possible effects of the intervention drug on the outcome, only participants randomized in the placebo groups were pooled for all analyses (*n* = 3775). See Figure 1 for a flow chart of participants.

Key exclusion criteria

Key exclusion criteria for participation in the WHI HT were the following: invasive cancer within the previous 10 years, major cardiovascular (myocardial infarction or stroke) disease events in the previous 6 months, medical conditions contraindicating for hormone therapy, systolic blood pressure > 200mmHg or diastolic blood pressure > 105mmHg. Key inclusion criteria for participation in the WHIMS were being 65 years or above and free of dementia. The Modified Mini-Mental Exam (3MSE) was used as a primary screening assessment of cognitive functioning (Teng & Chui, 1987) at baseline screening and then at annual follow-up visits. Those who scored below a set cutpoint at

baseline were excluded from analyses. Specifically, those with an education level > 9 years and who scored below 88 were excluded, and those with an education level ≤ 9 years and who scored below 80 were excluded. These cutpoint were based on previous studies (Graham & Rockwood, 1997; Tombaugh, McDowell, Kristjansson, & Hubley, 1996) and were applied throughout all WHI studies. Those who scored below their respective cutpoint at all time points were scheduled for a more extensive neurocognitive assessment and neuropsychiatric examination.

Data Analysis

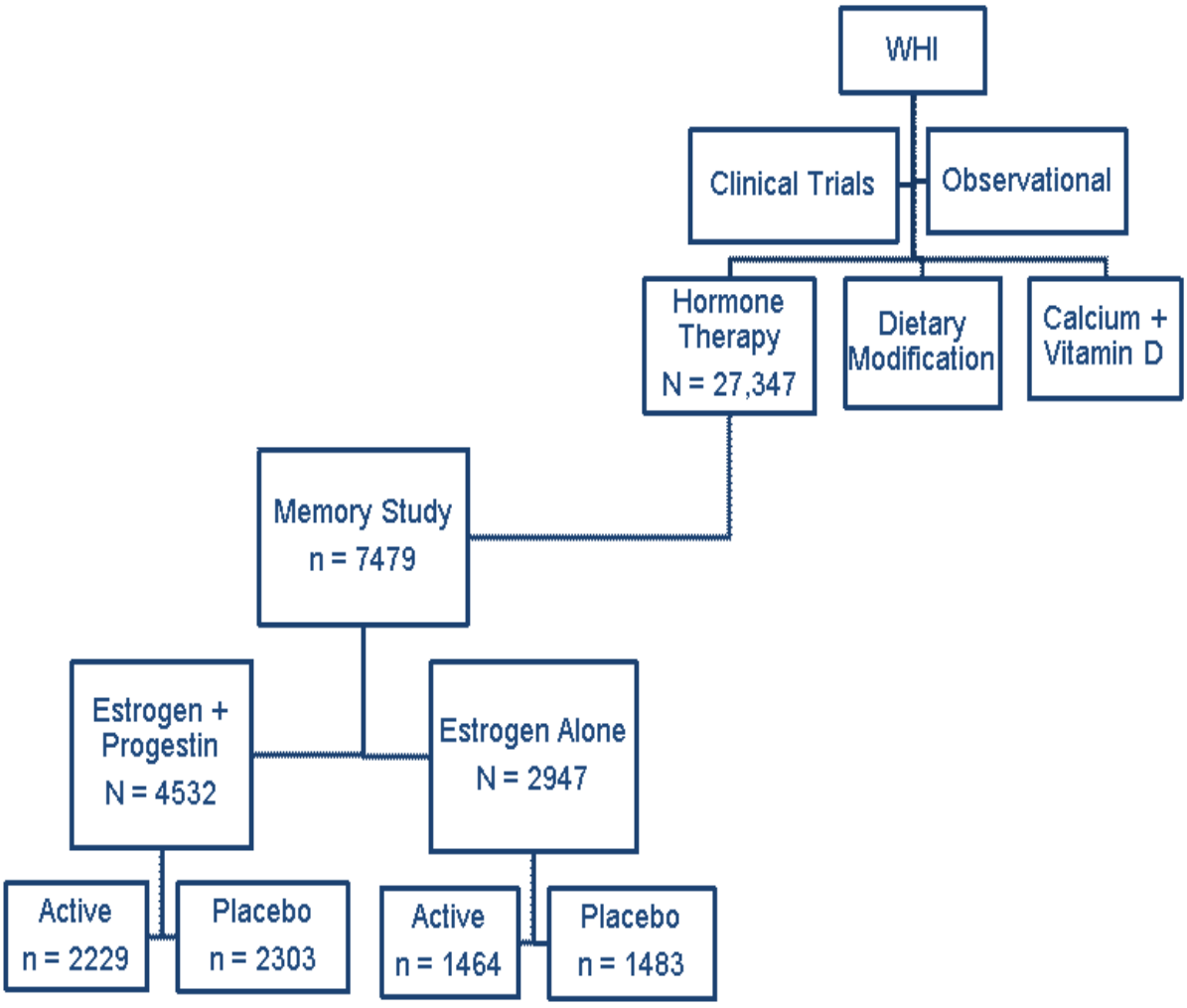
To address all prospective research questions, linear mixed effects models were used. These models combined fixed-effects regression methods and a generalization of the variance components (site-level factors and time). Covariates for the mixed models included race/ethnicity, age, SES, comorbidities, etc. Individual level variables were treated as fixed effects, and site-level factors and time as random effects.

Significance of the Research Project

In light of the inevitable process of major life events and the increased risk the stress these events may exert on individuals, consideration should be given to interventions or policies that attenuate the stress of major life events. As emerging evidence is just beginning to link the negative effects of stressful life events on cognition, more research is necessary to support the relationship between stressful life events and cognitive functioning. To the extent that stressful life events are deleterious to cognitive functioning, opportunities to promote protective health behaviors become imperative.

External and internal variables may be important mechanisms that buffer against the deleterious effects of stressful life events. However, the possible ameliorating role of these variables on the relationship between stressful life events and health outcomes, such as cognitive function, has yet to be examined. The investigation applied longitudinal analyses to examine the effects of stressful life events on the incidence of cognitive function decline. In addition, the possible moderating or mediating role of external and internal variables on the relationship between stressful life events and cognitive function were examined. Only one prior study has examined the prospective relationship between stressful life events and cognitive function. No previous study has examined the potential protective effect of external or internal factors to ameliorate the potential negative effects of stressful life events on cognitive function. Finding factors that may offset an individual's increased risk for developing dementia is critical for the successful implementation of public health interventions that have the potential of affecting a large proportion of the female population.

Figure 1. flow chart of WHI MS participants



CHAPTER 2: Examining the association between stressful life events and cognition

Background

Cognitive function

Subtle decrements in cognitive function predict future dementia and may be considered a marker of preclinical disease (Kawas et al., 2003). Dementia is a common geriatric syndrome that is marked by declines in memory and other cognitive functions that may ultimately lead to a loss of independent function (American Psychiatric Association, 2006). Alzheimer's disease is the most common form of dementia of people aged 65 and above (Hebert et al., 2003). In 2000, there were ~ 4.5 million individuals with Alzheimer's disease in the US (Hebert et al., 2003). With the impending retirement of the baby-boom cohort, the prevalence of Alzheimer's disease is expected to double by 2025 and nearly triple by 2050 (Hebert et al., 2003). Furthermore, the burden of disease is not equally distributed, as there are data to suggest women may be two to three times more likely than men to develop Alzheimer's disease (Birge, 1996).

While brain deterioration and cognitive decline are considered common characteristics of aging, not everyone experiences decline at the same rate and/or to the same degree. These individual differences in aged persons suggest that deterioration and decay is not an inevitable product of aging. Thus, research on risk factors and protective factors for diminished cognitive function in aged adults is of critical public health importance.

Stressful Life Events

Major life events are considered a measure of life stressors (Rahe, 1979). Major life event stressors are characterized by potentially high-impacting events, such as parents divorce or changing schools. The role that stressful life events play in the etiology of various diseases has been researched for the last three decades (Rabkin & Struening, 1976). It is hypothesized that excessive stress may play a role in the pathogenesis of chronic diseases in modern technological societies (Dodge & Martin, 1970; Greenwood, Muir, Packham, & Madeley, 1996a; McEwen, 2004). The underlying assumption is that the negative nature of events is not the important factor, but the amount of change that is required to readjust to a tolerable level of functioning.

Disease onset is generally thought to be influenced by a complex interaction of multiple factors, including the presence of stressful environmental conditions, perception by the individual that such conditions are stressful, the relative ability to cope with or adapt to these conditions, and a genetic predisposition to a disease (Rabkin & Struening, 1976). The potential negative effects of stress may likely be the result of at least three characteristics of the stressor: magnitude, intensity, and duration (McEwen, 1998). In this context the stress concept may greatly aid in explaining why some individuals are more susceptible to illness than others.

In cross-sectional and prospective investigations, modest but statistically significant relationships have been found between increasing life events and increased risk of disease (Kop, 1997; Pyykkönen et al.; Vitaliano et al., 2002; von Kanel, Dimsdale, Patterson, & Grant, 2003), depression (Kessler, 1997), and physical impairment

(Whitehead, Crowell, Robinson, Heller, & Schuster, 1992). However, very few studies have examined the association between stressful life events and cognitive functioning and only one study has prospectively examined the association between life events and declines in memory (Peavy et al., 2009).

Literature Review: stressful life events and cognition

Previous studies have examined the influence of real-life and laboratory stressors on physiological (Grant et al., 1989; Greenwood et al., 1996a) and psychiatric outcomes (Monroe, Slavich, Torres, & Gotlib, 2007; von Kanel et al., 2003) as well as cognitive functioning (Lee, Kawachi, & Grodstein, 2004; Peavy et al., 2009). Preliminary data seem to indicate that individuals exposed to higher levels of stressors have a modest increased risk for lower cognitive function scores. An earlier study used a laboratory controlled setting to examine the relation between stressful and nonstressful tasks on declarative/nondeclarative memory performance among older, healthy individuals (Lupien et al., 1997). Lupien and colleagues, using a cross-sectional data analysis, found that stressful experiences were associated with a reduction in word recall.

Fewer studies examined the association between life events and cognition. For instance, Rosnick et al. conducted a secondary data analysis using participants from the Charlotte County Healthy Aging Study, a larger, population-based sample of older adults. The investigators found that the sum score of a self-report checklist of recent negative life events was not associated with worse episodic memory performance; however, single items, such as the recent death of a sibling, were significantly

associated with worse performance (Rosnick, Small, McEvoy, Borenstein, & Mortimer, 2007). Peavy and colleagues investigated the prospective association between stressful life events and rate of memory decline among cognitively normal and mildly impaired older adults. In a sample of 102 older adult, they did not find a significant association between stressful life events and cognitive function decline among cognitively normal individuals. However, the authors cite methodological issues that could mostly explain contradictions of their results compared to others which did report an association between stressful life events and cognitive decline. Another study investigated the effect of major life events on working memory efficiency among university students and found that those reporting at least one life difficulty over the previous year recalled fewer words on a complex memory task compared to those reporting none (Wilding, Andrews, & Hejdenberg, 2007).

A major weakness of most of the studies using life events as the exposure (Lupien et al., 1997; Peavy et al., 2009; Wilding et al., 2007) is the small sample size (range: 14 -102). A limitation of most of these studies is that few have examined the relationship between stress and memory when both variables are measured repeatedly over time. Overall, only one study has longitudinally examined the relationship between stressful life events and cognitive performance (Peavy et al., 2009) and all the results are not congruent. Consequently, there is a void in the literature regarding the potential association between stressful life events and cognitive function decline, especially among a subpopulation of women who are at a period of life of considerable change. Considering the relevancy and somewhat unavoidable nature of stressful life

events, it appears prudent to examine its potential detrimental effects on cognition among a sample of older women.

Preliminary evidence suggests that stressful life events may be associated with negative health outcomes. However, only one previous study has investigated the prospective association of stressful life events on memory. Consequently, more data are needed to support the hypothesis that cumulative and repeated exposure of stressful life events are associated with lower cognitive functioning over time.

Purpose

The purpose of this study was to examine the relationship between stressful life events and corresponding changes in cognitive function. The aims of the study were addressed through the answering following research questions and hypotheses:

Research questions and hypotheses
R1: What is the cross-sectional association between aggregate and individual stressful life events and cognitive function? **H1:** Stressful life events will be negatively related to cognitive function. Specifically, individuals exposed to less or no stressful life events will have higher cognitive functioning scores, compared to those with high stressful life events.
R2: What is the prospective association between aggregate and individual stressful life events and cognitive function? **H2**: Stressful life events will be positively related to cognitive function decline. Specifically, individuals exposed to less or no stressful life events will have higher

cognitive functioning scores, compared to those with high stressful life events.

Methods

Theoretical Framework

The theoretical framework used to inform the biological mechanism through which stressful life events may affect cognition is based on the stress response model. Stress may be defined as a response to an event that evokes a stress response and strains an individual's ability to handle imposed demands (R. S. Lazarus & Folkman, 1984). Stressors are relative and specific to the individual. For instance, an individual's perception of a threatening event, whether real or not, is pivotal in the process whereby stress affects health (Cohen et al., 1983). When the brain perceives an event as threatening, a coordinated set of physiologic and behavioral responses, involving the autonomic, neuroendocrine, metabolic and immune systems, are initiated (Lupien, McEwen, Gunnar, & Heim, 2009). Over time, exposure to chronic stress can accumulate, and the overexposure to mediators of the aforementioned systems may have adverse effects on these organ systems, leading to disease (Lupien et al., 2009; Sapolsky, 1996).

Design

Data from the Women's Health Initiative Memory Study (WHIMS; *n* = 7,479), a subset of participants randomly selected from the WHI Hormone Therapy Trial (WHI HT), were used to address all specific questions. The WHI is a large, multicenter investigation of postmenopausal women enrolled in one of the 3 randomized clinical trials (Hormone Therapy, Diet Modification or Calcium Vitamin D) or the Observational Study. The WHI was initiated in 1992 and enrolled participants at one of 40 WHI clinical

centers nationwide. Participants were followed annually up to 8.5 years (*M* = 5.2 yrs). The WHI HT was stopped early due to the unfavorable risk-to-benefit ratio and evidence of early harm (Writing Group for the Women's Health Initiative Investigators, 2002). The decision to stop the WHI HT also ended WHIMS.

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To control for the possible effects of the intervention drug on the outcome, only participants randomized in the placebo groups were included for all analyses (*n* = 3,775). Table 1 provides samples sizes for each group by data collection point. In addition, we only used data from 5 data collection points (baseline and follow-up years 1 through 4) due to the significant loss to follow-up after year 4.

Participants

To address all research questions, complete data on healthy women aged 65-79 years enrolled the WHI HT and the WHIMS were available. Of these combined cohorts, complete data were available for approximately *n* = 3,775 healthy women who did not receive an active treatment.

Key exclusion criteria for participation in the WHI HT were the following: invasive cancer within the previous 10 years, major cardiovascular (myocardial infarction or stroke) disease events in the previous 6 months, medical conditions contraindicating for hormone therapy, systolic blood pressure > 200mmHg or diastolic blood pressure > 105mmHg. Key inclusion criteria for participation in the WHIMS were being 65 years or above and free of dementia. The Modified Mini-Mental Exam (3MSE) was used as a primary screening assessment of cognitive functioning (Teng & Chui, 1987) at baseline screening and then at annual follow-up visits. Those who scored below a set cutpoint, which were based on previous studies (Graham & Rockwood, 1997; Tombaugh et al., 1996), were scheduled for a more extensive neurocognitive assessment and neuropsychiatric examination.

Measures

All of the measures in this application have already been assessed on the WHI HT and WHIMS cohorts and are available through the public use data sets.

Dependent variable

Cognitive function

Global cognitive function was based on scores from the 3MSE collected at baseline and annually for up to 8 years. The 3MSE consists of 15 items that produce a range of possible scores from 0-100, with higher scores reflecting better cognitive functioning. The 3MSE, a quantitative indicator of cognitive function widely used clinically and epidemiologically, has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia (Bravo & Herbert, 1997; McDowell,

Kristjansson, Hill, & Hébert, 1997). A score of < 88 on the 3MSE has been suggested as the optimal cutpoint to classify this sample of women (with education levels ≥ 9 years) with probable dementia or composite mild cognitive impairment/probable dementia, and a score of < 80 for those with < 9 years of education. Trained and certified technicians, who administered the 3MSE in the WHIMS, were masked to the treatment assignment of all participants.

Independent variable

Stressful life events

Participants completed a modified version of the stressful life events scale from the Alameda County Epidemiologic Study (Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984). This inventory was modified to ensure relevance to older women. The questionnaire was completed at baseline and again at all follow-up points for up to seven years.

Participants responded yes or no as to whether any of 11 life changes had occurred over the past year: spouse died, spouse had serious illness, close friend died, had major problems with money, divorced or break up, close friend divorced, major conflict with children or grandchildren, lost job, physically abused, verbally abused, and pet died. Positive responses were summed, yielding a score ranging from 0 to 11 with a higher score indicating more life events. A previous study using participants from the WHIMS reported that women on average reported slightly less than two stressful life events (M = 1.7, SD = 1.4) per year (Michael et al., 2009). The sum score of this scale was considered unweighted.

In addition, women were asked to appraise each life event that occurred based on the amount of upset that it caused based on a scale ranging from 1 (*did not upset me*) to 3 (*upset me very much*) in the past year. This scale ranged from 0 to 33 with a higher score indicating a participant experienced a greater number of more stressful events (M = 3.3, SD = 3.2; (Michael et al., 2009). The sum score of this scale was considered weighted.

Analyses included several separate assessments of stress: 1) each individual item on the checklist were assessed for its association with cognition; 2) an unweighted sum score to determine if individual items or the total index is associated with cognitive function decline; and 3) a weighted sum score to determine if individual items or the total index is associated with cognitive function decline; 4) a cumulative assessment of a participant being exposed to at least three stressful life events at every time point.

The individual assessments of stress were chosen based on results from previous studies that found significant associations between individual measures and health outcomes. In order to best capture the cumulative effects of repeated exposure to stressful life events, the stressful life events variable was dichotomized into two groups: those who were exposed to three or more stressful life events at all data collection points and those who were exposed to less than three. We chose a cutpoint of three stressful life events because we hoped to define those exposed to high levels of stress.

Covariates

Sociodemographics

Age, r*ace/ethnicity*, *education and insurance status* were assessed via self-report questionnaires. Women self-identified as non-Hispanic white, black or African American, Hispanic or Latino, Asian/Pacific Islander, American Indian or Alaska Native, or other. Participants indicated one of 11 categories of educational attainment: Didn't go to school, Grade school (1-4 years), Grade school (5-8 years), Some high school (9-11 years), High school diploma or GED, Vocational or training school, Some college or Associate Degree, College graduate or Baccalaureate Degree, Some post-graduate or professional, Master's Degree, or Doctoral Degree.

Psychosocial factors

Social support. Nine social support items were selected from the larger 19-item Medical Outcomes Study (MOS). The social support questionnaire indicated perceived availability of the components of functional support (Sherbourne & Stewart, 1991).

Behavioral factors

*Smoking***.** Participants indicated number of cigarettes usually smoked each day. *Smoking history*. If participants indicated they were ever a regular smoker, they were asked how many years they were a regular smoker. Participants also indicated the number of years they lived with a smoker as a child. *Alcohol consumption*. Alcohol consumption was determined from responses to a single two-part item. The first part categorized alcohol intake on a weekly/monthly level; the second part asked participants to indicate number of servings per week of beer, wine and/or liquor based

on a medium serving size which is 12oz of beer, 6oz of wine and 1½ oz of liquor.

Antidepressant Use. To measure antidepressant use, participants were asked to bring all current medications to baseline interviews (WHI Clinical Coordinating Center).

Comorbid conditions and physical factors

Diabetes. Participants self-reported if a physician had ever told them that they had "sugar diabetes" when they were not pregnant. Family history of diabetes was also be ascertained. *Body mass index (BMI).* BMI was measured by trained research personnel and calculated from height and body weight as follows: BMI (kg/m^2) = Body weight (kg) / Height $(m)^2$ and was used to classify subjects as normal weight, at risk for overweight or overweight using the cutpoints as recommended by the U.S. Centers for Disease Control and Prevention Centers for Disease Control and Prevention. *Depression*. Depressive symptoms were measured using the 6-item scale from the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977). *Cardiovascular disease.* Family history of cardiovascular disease was also ascertained.

Data are not available on family history of dementia. Unfortunately, apolipoprotein E4 levels of WHIMS participants were not available in the public use data set. Thus, it was not possible to test for a possible interaction between these factors and stressful life events on cognitive function decline.

Analysis

To address R1 and R2, a linear mixed effects model, which combined fixed-effects regression methods (placebo group and covariates) and a generalization of the variance components (site-level factors and time), was applied.

Since stressful life events were also collected at several time points, individual rates of change for each participant were obtained. To this effect, mixed effects linear models were fit with stressful life events as a function of time (for each data collection point), with a random participant-specific intercept and slope added to the model. All informative slopes (i.e., statistically significant) were used in analyses as estimates of rates of stressful life events. For instance, participants were divided into three categories according their time-varying slopes for stressful life events: increasing, decreasing or no change. Individuals who show a positive slope (i.e., stressful life events score increases from baseline to last data collection period) were categorized as an "increasing" group for stress. Those who have a decreasing slope (i.e., stressful life events score decreases from baseline to last data collection period) were categorized as a "decreasing" group for stress. Those who have a flat slope (i.e., stressful life events score remains relatively steady from baseline to last data collection period) were categorized as a "no change" group for stress.

Odds ratios were calculated to indicate whether individuals had an increased or decreased odds of scoring below the established cutpoint. Two different cutpoints were applied, based on educational attainment, as stipulated by WHI investigators. For those

with < 9 years of education, the cutpoint was 80; for those with ≥ 9 years of education, the cutpoint was 88.

Covariates for the mixed models included race/ethnicity, age, year of data collection, SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease. Individual-level factors (e.g., SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease) were treated as fixed effects, and site-level factors and time were treated as random effects.

Linear mixed models

Linear mixed effects models were run using SAS PROC MIXED, which supports mixed effects models.

R1: What is the cross-sectional association between aggregate and individual stressful life events and cognitive function? **H1:** Stressful life events will be negatively related to cognitive function. Specifically, individuals exposed to less or no stressful life events will have higher cognitive functioning scores, compared to those with high stressful life events.
R2: What is the prospective association between aggregate and individual stressful life events and cognitive function?

H2: Stressful life events will be positively related to cognitive function decline. Specifically, individuals exposed to less or no stressful life events will have higher cognitive functioning scores, compared to those with high stressful life events.

For cognitive function (CF), let CF_{ijk} denote for observation *i* at time *j* at site *k,* the linear mixed model can be written:

$$CF_{ijk} = \alpha + \beta_1 * LE_{ijk} + \beta_2 * time_{ik} + \beta_3 * \text{covariate}_{ijk} + \gamma_{i0} + \gamma_{i1} * time_{ik} + \gamma_{i2} * site_{ik} + \varepsilon_{ijk}$$

Where $\gamma_{i0} \sim N\left(0, \sigma^2_{\text{int}\,ercept}\right), \gamma_{i1} \sim N\left(0, \sigma^2_{time}\right), \gamma_{i2} \sim N\left(0, \sigma^2_{site}\right)$

Note. LE = life events.

Results

Table 1.1 presents the variable of interest. Tables 1.2 and 1.3 displays the baseline characteristics of the participants randomized into the placebo arms from both clinical hormone therapy clinical trials. The average age at baseline for this combined sample was 70.1 (*SD* $\pm$ 3.85) years. The most often reported income was $20,000 to $34,999 (30%) and 53% of the sample were married or in a marriage-like relationship. Based on BMI, 29% of this sample had a BMI within the normal range (i.e., BMI = <25) while 35.9% were overweight (BMI = 25-29.9) and 34.4% were obese (BMI $\geq$ 30; data not shown). Approximately 66% of the sample had at least some college education. In addition, 53% of the women never smoked cigarettes and 63% did not provide informal care for an ill friend or spouse. The most often reported stressful life event was having a friend die or become seriously ill (45%), followed by having an ill spouse/partner (28%), and having money problems (26%).

Cross-sectional associations between stressful life events and cognitive function

Age-adjusted models assessing the cross-sectional association between each measure of stress reveal significant relationships at all time periods (Table 1.4). All associations were in the expected direction. For instance, those exposed to a stressful life event had lower cognition scores compared to those not exposed. In all the age-adjusted only models, five stress variables were associated with cognition scores: unweighted stressful life events sum score, weighted stressful life events sum score, exposure to an ill spouse, exposure to a spouse dying, and exposure to three or more life events at all time periods. These associations were significant across all time points,

with effect sizes ranging from 0.10 – 2.08, meaning exposure to certain stress variables were associated with lower scores on the 3MSE. The difference of 3MSE scores were as small as 0.10 of a point to as high as a 2-point difference. However, after adjusting for all covariates, only exposure to an ill spouse was significantly associated with lower cognition scores across all data collection periods. Exposure to a spouse/partner dying and three or more life events was significantly associated with lower cognition scores at two data collection periods.

When SES factors were taken into account, several significant relationships remained at select time points. It appears that not reporting a seriously ill spouse was most consistently associated with higher cognitive function scores relative to those reporting a seriously ill spouse at four time points, baseline through year 4. The next most consistent stress variable associated with higher cognitive function scores is the cumulative effect of life events, i.e., < 3 stressful life events per year. Those reporting fewer than 3 stressful life events per year, compared to those reporting at least 3, appeared to have higher cognitive function scores at 3 time points, baseline through year 2. The average magnitudes over the significant time periods for the variables <3 life events and ill spouse ($\overline{X}_{\beta}$ = 0.73 and 0.58, respectively) appear relatively modest especially when considering the smaller variance in the change in cognitive function scores.

In the case of the weighted and unweighted scales of stressful life events, higher levels of stress were associated with lower cognitive function scores compared to those with lower levels of stress. Two measures, spouse dying and cumulative exposure to at

least three stressful life events per year, appeared to have the highest average magnitude over all time periods ($\overline{X}_{\beta}$ = 1.22 and 1.16, respectively). In other words, those who did not have a spouse die compared to those who did have a spouse die had significantly higher cognitive function scores, and likewise for those who recorded less than three stressful life events compared to those who had at least three per year. Considering the mean change of this sample's cognitive function score remained steady over all data points, these magnitudes appears relatively modest.

Longitudinal associations between stressful life events and cognitive function

Table 1.5 presents results of several multivariate, mixed effects models that examined the prospective association between the five assessments of stress and cognitive function. All stress variables were significantly associated with cognitive function, and in the hypothesized direction, for the age-adjusted models. Specifically, for every one point increase in the unweighted stressful life events sum score there was a 0.21 decrease in cognitive function score ($p < 0.0001$).

When SES variables were included in the models, three stress variables remained statistically significant: <3 life events, spouse dying, and spouse ill. The beta estimates appear to have been attenuated slightly, indicating a confounding effect for SES. There is a similar pattern of significant associations when controlling for age, SES, and comorbidities. Further adjustment of social support variables appeared to reduce the number of significant stress variables associated with lower cognitive function scores. For instance, those who did not report a spouse dying had on average higher cognitive

function scores than those who did report a spouse dying

($\beta = 0.68, SE = 0.12, p < 0.0001$).

In the final model, when all previous significant confounders were entered into the model, only two stress variables remained statistically significant: <3 life events ($\beta = 0.61, SE = 0.24, p = 0.019$) and spouse ill ($\beta = 0.68, SE = 0.12, p < 0.0001$). Specifically, those who reported less than 3 stressful life events at all time periods scored on average 0.61 higher than those reporting at least 3 stressful life events at all time periods.

Odds ratios (ORs) were also calculated to provide perspective regarding the odds of an individual scoring below her respective cutpoint on the 3MSE. For those with < 9 years, the cutpoint was 80; for those with $\geq$ 9 years, the cutpoint was 88. For those with > 9 years of education, the odds of scoring below 88 was 56% (OR = 1.56, 95% Confidence Interval [CI] = 1.02, 2.40) greater for those who reported having at least 3 stressful life events at all time periods compared to an individual who did not report at least 3 stressful life events at all time periods, after controlling for all covariates. The odds of scoring below the cutpoint for those with < 9 years of education were not statistically different between those who were exposed to at least 3 stressful life events at all time periods and those who were not (OR = 1.16, CI = 0.56, 2.50).

A similar effect was seen regarding exposure to an ill spouse. For those with $\geq$ 9 years of education, the odds of scoring below 88 was 2.19 (95% CI = 1.72, 2.78) greater for those who reported having an ill spouse compared to an individual who did not report an ill spouse, after controlling for all covariates. The odds of scoring below the

cutpoint for those with $\geq$ 9 years of education were not statistically different between those who were exposed to an ill spouse and those who were not (OR = 1.11, CI = 0.63, 1.95).

It should be noted that the magnitude of the relationships (i.e., beta estimates) for each of these stress assessments remained relatively steady throughout all modeling stages. As with what was indicated by the cross-sectional analyses, the relative magnitude of associations between higher reported levels of stress and lower cognitive function score appears modest for a sample that displayed no statistically significant changes in the 3MSE.

In order to best depict the relationship between stressful life events and cognition, individuals were divided into three categories according their time-varying slopes for stressful life events: increasing, decreasing or no change. Results revealed significant group differences such that those with an increasing slope had significantly lower cognitive function scores than those who decreased over time.

Discussion

The primary purpose of this study was to examine the cross-sectional and longitudinal relationship between several distinct stressors on cognitive function. For our first hypothesis, we predicted that stressful life events would have a negative association with cognitive function in cross-sectional analyses. Specifically, individuals exposed to more stressful life events, aggregately and individually, would have lower scores on cognitive functioning, compared to those with low or no stressful life events at each data collection point. Consistent with our hypothesis, data from the

multivariate models indicate that not reporting an ill spouse and having fewer then 3 stressful life events were consistently associated with higher cognitive function scores than those reporting an ill spouse and having at least 3 stressful life events. It should be noted that our sample appeared to be a highly educated, high functioning group of postmenopausal women. Hence, these results may not be generalizable to a lower functioning group of women with lower educational attainment.

There are only three previous studies (Peavy et al., 2009; Rosnick et al., 2007; Wilding et al., 2007) that examined the relationship between stressful life events and cognition. For the most part, our cross-sectional findings are consistent with previous studies. Specifically, higher sum scores on the stressful life events checklist was not consistently associated with lower cognitive function scores, after adjusting for SES factors. Unlike the previous studies, our results indicated that a single item on the checklist (an ill spouse) was consistently associated with lower cognitive function scores. In contrast, data from Rosnick and colleagues (Rosnick et al., 2007) indicated that individuals who highly rated the effect of an injury or illness of a friend during the past year performed better on all three cognitive tasks (episodic memory, attention, and psychomotor speed). Thus, our results still offer repeatability and consistency that stressful life events may have an effect on cognitive function.

In addition, we used a cumulative assessment of stressful life events, which other studies have not used. This cumulative assessment, $\geq$3 stressful life events per year, was also associated with lower cognitive function scores compared to those who reported less than 3 stressful life events per year. To our knowledge, no previous

studies have used this measure of stressful life events. Hence, our results add to the literature, suggesting that there might be a cumulative effect and a threshold by which stressful life events negatively affect cognition.

For our second hypothesis, we predicted that stressful life events would have a negative association with cognitive function in a prospective analysis. Specifically, individuals exposed to more stressful life events, aggregately and individually, would have lower scores on cognitive functioning, compared to those with low or no stressful life events. Results from the mixed effects models appear to indicate that reporting an ill spouse and reporting at least 3 stressful life events at all data points were associated with significantly lower cognitive function scores compared to those not reporting an ill spouse and less than 3 stressful life events, respectively. When individuals were categorized based on their stressful life events slope, our results revealed significant group differences, such that those with an increasing slope had significantly lower cognitive function scores than those who decreased over time.

Only two previous studies have examined the prospective association between stressful life events and cognition (Peavy et al., 2009; Rosnick et al., 2007). However, both studies did not find a significant association between life stress ratings and accelerated cognitive decline in cognitively normal subjects. The reason for contrasting results may be in part due to methodological issues. For instance, all previous studies operationalized stressful life events and cognitive function differently and we were the only study to limit our sample to older women. However, the sample sizes for Peavy and colleagues (n = 52) and Rosnick and colleagues (N = 428) for longitudinal analysis of

the previous studies were relatively smaller than the sample used for analysis in this study; hence we had more power in order to detect significant relationships.

Biologic Plausibility of Life Events Stress and Cognitive Function

Biologic evidence suggests that stress may be associated with cognitive function. Specifically, the repeated release of cortisol, a stress hormone, is hypothesized to suppress the functional ability of the hippocampus, an area of the brain integral for the maintenance and processing of memories. Over time, high levels of circulating cortisol may lead to hippocampal atrophy (McEwen & Seeman, 1999). It is thought that the repeated release of glucocorticoids, due to chronic exposure to stress, may negatively affect brain function, especially in the hippocampus (McEwen, De Kloet, & Rostene, 1986). The hippocampus is widely regarded as an integral structure for declarative memory and is responsible for regulating the stress response by inhibiting the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress (McEwen, 1998; McEwen & Sapolsky, 1995; Squire, 1992). In addition, the hippocampus is hypothesized to be a prime area targeted for detecting dementia because of its high concentrations of cortisol receptors (Herman & Cullinan, 1997). Impairment of the hippocampus is thought to decrease the reliability and accuracy of memories (Herman & Cullinan, 1997; McEwen, 1998; McEwen & Sapolsky, 1995).

What this study adds

In the current study, we investigated cross-sectionally and longitudinally if exposure to individual and aggregate measures of stressful life events were associated with cognition among post-menopausal women without cognitive impairment. By

investigating how changes in stressful life events over time are related to changes in cognition, results from this study may be able to improve upon the current literature by: 1) elucidating the impact of relevant and unavoidable risk factors on future cognition (e.g., stressful life events); and 2) providing useful information on risk factors that may influence the development of cognitive function decline.

Strengths and limitations

There were several strengths of this study. We used a nationally representative sample of post-menopausal women who were enrolled in the largest randomized clinical trial of hormone replacement therapy. In order to eliminate effects of any intervention, only participants randomized into the placebo arms were used. Due to the relatively large sample size and multiple follow-up points, we were able to use mixed effects modeling, a statistical analysis that incorporated all data points (up to 4 years) for both the exposure and outcome variables. Unlike similar previous studies, we were also able to adjust for many confounders, such as social support, comorbidities, physical markers (e.g., BMI, blood pressure), and behavioral variables (e.g., smoking, alcohol drinking).

In spite of the study strengths, several limitations need to be acknowledged. Operationalizing stress as exposure to life events assumes that these events are perceived as negative and undesirable. Although this approach has a subjective component, it is less liable to reporting bias and variations (Phillips, Der, & Carroll, 2008). Stressful life events also assesses multiple domains of events, including financial worries to bereavement. Since the stressful life events scale used for this study also

employs a weighted measure to ascertain participants' perceived impact of the life events, the psychosocial stress load (overall impact of stressful life events) may perhaps be more accurately captured (Holmes & Rahe, 1967). Further, our sample appeared to be a well-educated, highly functioning group. As such, there was not much variance regarding cognitive function scores. Hence, our results may not be applicable to the general population.

The secondary nature of data analyses are limited to what was collected during the data collection points. Consequently, operationalization of all measures was based on decisions made by WHI investigators. Assessment of all variables involved in addressing our specific research questions may not be ideal and not all possible confounding variables may be available. The most notable is not being able to control for the APO e4 allelle.

In addition, certain biases may have been introduced due to the prospective nature of the clinical trials. Specifically regarding recruitment and enrollment of minority women, data were not collected on the total number of women contacted or on women who chose not to make the initial contact. Therefore, it is impossible to discern differences between racial/ethnic groups with regard to willingness to participate in the WHI trials. While our sample appeared to be a highly functioning, well educated group, nonetheless our results indicate that repeated exposure to certain life events may pose a risk in the maintenance of cognitive function skills.

Conclusion

Considering the number of individuals ≥ 65 years is set to dramatically increase as the baby boom generation ages and the prevalence of Alzheimer's disease is expected to double by 2025 and nearly triple by 2050 (Hebert et al., 2003), elucidating risk factors for cognitive function decline has become imperative. Our results appear to lend support that exposure to certain life events and repeated exposure of stressful life events are associated with lower cognitive functioning over time among a representative sample of post-menopausal women.

Results Tables

Table 1.1: Study Variables and Instruments

Variable	Instrument
Independent Variable	
Stressful life events	Questionnaire
Covariates	
Sociodemographics	Questionnaire
Psychosocial	
Depression	CES-D
Social support	MOS
Behavioral	
Smoking	Questionnaire
Alcohol consumption	Questionnaire
Medical	
Cardiovascular disease	Questionnaire
Diabetes	Questionnaire
BMI	Questionnaire
Dependent Variable	
Cognitive function	3MSE

Table 1.2. Stressful life events and cognition by year

Variable (%)	Baseline	Year 1	Year 2	Year 3	Year 4
Spouse die					
No	93.9	93.9	93.8	93.5	94.1
Yes	6.1	6.1	6.2	6.5	5.9
Spouse ill					
No	72.1	72.1	73.3	73.9	75.9
Yes	27.9	27.9	26.7	26.1	24.1
Friend die/seriously ill					
No	54.9	54.9	54.9	54.7	55.8
Yes	45.1	45.1	45.1	45.3	44.3
Major money problems					
No	73.6	76.4	76.6	76.3	78.4
Yes	26.4	23.6	23.4	23.7	21.6
Divorce or breakup					
No	97.9	99.3	99.5	99.5	99.6
Yes	2.1	0.7	0.5	0.5	0.4
Close friend/family have a divorce					
No	86.4	89.3	89.4	89.9	89.5
Yes	2.2	10.7	10.6	10.1	10.5
Have major conflict with children					
No	81.7	86.4	86.5	86.9	87.5
Yes	18.3	13.6	13.5	13.1	12.5
Have a major accident or disaster					
No	94.2	94.7	94.4	94.7	94.6
Yes	5.8	5.3	5.6	5.3	5.4
Did you, family, or friend lose job or retire					
No	80.8	86.4	85.8	85.9	85.8
Yes	19.2	13.6	14.2	14.1	14.2
Physically abused					
No	99.1	99.4	99.5	99.5	99.5
Yes	0.9	0.6	0.5	0.5	0.5
Verbally abused					
No	91.5	93.8	93.9	93.7	99.5
Yes	8.6	6.2	6.1	6.3	0.5
Pet die					
No	92.2	93.4	93.0	93.5	94.5
Yes	7.8	6.6	7.0	6.5	5.5
Mean cognitive function (SD)	95.2 (4.3)	95.9 (4.0)	96.3 (4.1)	96.5 (3.9)	96.6 (4.3)

Table 1.3: Baseline sample characteristics and demographics

	Total	Spouse ill		< 3 life events	
Variable		No	Yes	No	Yes
Mean cognitive function score (SD)	96.3 (4.07)	95.4 (4.10)	95.1 (4.53)	95.3 (4.23)	94.0 (5.00)
Mean age (years, (SD))	70.1 (±3.85)				
Ethnicity/Race (%)					
American Indian or Alaskan Native	0.4	0.3	0.0	0.3	0.0
Asian or Pacific Islander	1.6	0.3	0.0	1.5	0.1
Black or African-American	7.2	6.3	0.5	6.4	0.4
Hispanic/Latino	2.3	1.8	0.4	2.0	0.2
White (not of Hispanic origin)	87.2	82.7	4.9	83.7	3.9
Other	1.4	1.3	0.2	1.4	0.1
Level of Education (%)					
< High school	26.2	13.1	13.4	24.8	1.7
High school diploma or GED	7.4	3.7	4.0	7.0	0.8
Some college	35.2	16.5	18.6	33.0	2.1
≥ 4 years college	31.1	15.0	15.7	29.0	1.7
Income (%)					
< $19,999	27.0	13.1	14.3	25.0	2.4
$20,000 to $34,999	29.9	14.3	15.5	28.3	1.5
$35,000 to $49,999	20.0	9.5	10.4	18.7	1.2
≥ $50,000	23.1	11.5	11.5	21.8	1.2
Marital status (%)					
Never married	3. 6	1.9	1.5	3.4	0.1
Divorced or separated	12.2	6.7	5.5	11.0	1.2
Widowed	30.4	16.9	13.8	28.5	2.3
Presently married/marriage-like	52.9	22.8	30.9	51.0	2.7
Smoking status					
Never Smoked	52.9	49.4	3.5	50.5	2.4
Past Smoker	7.2	37.8	2.1	37.9	2.0
Current Smoker	39.9	6.8	0.4	6.7	0.5

Table 1.3 (cont.): Baseline sample characteristics and demographics

	Total	Spouse ill		< 3 life events	
Variable		No	Yes	No	Yes
Living alone					
No	60.1	57.6	2.3	56.7	3.2
Yes	39.9	36.3	3.8	38.5	1.7
Number of times per week a participant currently helps a friend or family member					
No	63.4	59.3	4.4	61.3	2.4
Less than once a week	7.5	7.3	0.5	7.4	0.3
1-2 times a week	13.5	12.9	0.6	12.7	0.9
3-4 times a week	4.3	4.0	0.2	4.05	0.2
5 or more times a week	11.4	10.4	0.4	9.9	0.9

Table 1.4. Cross-sectional results of multivariate analysis.

Variable	Baseline		Year 1		Year 2		Year 3		Year 4	
	β	SE	β	SE	β	SE	β	SE	β	SE
Model 1: Age-Adjusted										
Life Event sum score (unweighted)[1]	**-0.30******	0.06	**-0.26******	0.06	**-0.26******	0.06	**-0.16******	0.06	**-0.17******	0.06
Life Event sum score (weighted)[2]	**-0.17******	0.03	**-0.15******	0.03	**-0.16******	0.03	**-0.10*****	0.03	**-0.10******	0.03
3+ Life events[a]	**-1.41******	0.29	**-1.40******	0.31	**-1.31******	0.32	**-0.84******	0.32	**-0.85***	0.36
Spouse die[b]	**-2.08******	.033	**-0.59***	0.26	**-1.24******	0.29	**-1.22******	0.27	**-0.96****	0.32
Spouse ill[b]	**-0.28***	0.14	**-0.75******	0.15	**-0.72******	0.16	**-0.75******	0.15	**-0.41***	0.18
Model 2: Age + SES-Adjusted										
Life Event sum score (unweighted)[1]	**-0.13***	0.05	-0.03	0.04	-0.06	0.05	0.03	0.05	0.06	0.06
Life Event sum score (weighted)[2]	-0.05	0.03	-0.03	0.02	**-0.05***	0.03	0.00	0.03	0.01	0.03
3+ Life events[a]	**-0.74****	0.26	**-0.65***	0.27	**-0.79****	0.29	-0.36	0.30	-0.30	0.33
Spouse die[b]	**-1.22******	0.30	-0.39	0.25	-0.50$^{\#}$	0.26	**-0.59***	0.26	-0.23	0.30
Spouse ill[b]	**-0.26***	0.13	**-0.64******	0.14	**-0.65******	0.15	**-0.75******	0.15	**-0.33**$^{\wedge}$	0.17

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$; $^{\wedge}p = 0.055$; $^{\#}p = 0.06$.

[1]Unweighted scale, higher score indicates more stressful life events (range: 0-11).

[2]Weighted Scale, higher score indicates more stressful life events (range: 0-33).

[a]Respondents who had < 3 stressful life events at all time periods were the reference; [b] "No" responders were the reference.

SE = Standard error. SES covariates include year, ethnicity/race, education, income, cohabitation status, alcoholic intake per week, smoking, marital status, and caregiving responsibilities.

Comorbidity covariates include BMI (as a continuous variable), cardiovascular disease, diabetes, depression, and blood pressure.

Table 1.4 (cont.). Cross-sectional results of multivariate analysis.

Variable	Baseline		Year 1		Year 2		Year 3		Year 4	
	β	SE	β	SE	β	SE	β	SE	β	SE
Model 3: Model 2 + Social support										
Life Event sum score (unweighted)[1]	-0.13	0.05	-0.01	0.06	-0.07	0.05	-0.05	0.06	-0.08	0.06
Life Event sum score (weighted)[2]	-0.06	0.03	-0.05	0.03	-0.03	0.03	-0.01	0.03	-0.03	0.04
3+ Life events[a]	**-0.66****	0.28	**-0.67***	0.30	**-0.63***	0.32	-0.33	0.36	-0.33	0.34
Spouse die[b]	**-1.10****	0.31	-0.33	0.27	-0.28	0.28	**-0.60***	0.27	-0.23	0.31
Spouse ill[b]	**-0.29***	0.13	**-0.62*****	0.15	**-0.59*****	0.15	**-0.93*****	0.16	**-0.31**$^{\#}$	0.17
Model 4: Model 3 + comorbidities										
Life Event sum score (unweighted)[1]	-0.01	0.05	-0.02	0.05	-0.07	0.05	-0.04	0.06	-0.09	0.06
Life Event sum score (weighted)[2]	-0.06	0.03	-0.03	0.03	-0.04	0.03	-0.01	0.03	-0.02	0.04
3+ Life events[a]	**-0.75****	0.27	**-0.56***	0.38	-0.64	0.30	-0.33	0.31	-0.29	0.32
Spouse die[b]	**-0.95****	0.33	-0.24	0.29	-0.12	0.30	**-0.72***	0.29	-0.21	0.33
Spouse ill[b]	**-0.61***	0.14	**-0.27*****	0.13	**-0.63*****	0.14	**-0.76*****	0.15	**-0.25**$^{\#}$	0.14

$p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$; $^{\#}p = 0.06$.

[1]Unweighted scale, higher score indicates more stressful life events (range: 0-11).

[2]Weighted Scale, higher score indicates more stressful life events (range: 0-33).

[a]Respondents who had < 3 stressful life events at all time periods were the reference; [b] "No" responders were the reference.SE = Standard error.

SES covariates include year, ethnicity/race, education, income, cohabitation status, alcoholic intake per week, smoking, marital status, and caregiving responsibilities.

Comorbidity covariates include BMI (as a continuous variable), cardiovascular disease, diabetes, depression, and blood pressure.

Table 1.5. Longitudinal results of mixed effects analysis.

Variable	β	SE	*p*-value
Model 1: Age-Adjusted			
Life event sum score (unweighted)[1]	**-0.21**	**0.05**	**<.0001**
Life event sum score (weighted) [2]	**-0.11**	**0.02**	**<.0001**
3+ Life events[a]	**-1.28**	**0.25**	**<.0001**
Spouse die[b]	**-0.59**	**0.24**	**0.007**
Spouse ill[b]	**-0.70**	**0.13**	**<.0001**
Model 2: Model 1 + SES			
Life event sum score (unweighted)[1]	-0.02	0.04	0.655
Life event sum score (weighted) [2]	-0.03	0.02	0.130
3+ Life events[a]	**-0.68**	**0.22**	**0.002**
Spouse die[b]	**-0.40**	**0.20**	**0.052**
Spouse ill[b]	**-0.61**	**0.11**	**<.0001**
Model 3 (Full Model): Model 1 + Model 2 + Comorbidities			
Life event sum score (unweighted)	0.01	0.04	0.839
Life event sum score (weighted)	-0.02	0.02	0.441
3+ Life events[a]	**-0.65**	**0.23**	**0.005**
Spouse die[b]	**-0.50**	**0.21**	**0.024**
Spouse ill[b]	**-0.60**	**0.12**	**<.0001**
Model 4: Model 1 + Model 2 + Social Support			
Life event sum score (unweighted)	0.03	0.04	0.457
Life event sum score (weighted)	-0.00	0.02	0.859
3+ Life events[a]	**-0.62**	**0.24**	**0.019**
Spouse die[b]	-0.33	0.23	0.168
Spouse ill[b]	**-0.68**	**0.12**	**<.0001**
Model 5 (Full Model): Model 4[†] + Comorbidities[†]			
Life event sum score (unweighted)	0.05	0.04	0.247
Life event sum score (weighted)	0.01	0.02	0.755
3+ Life events[a]	**-0.61**	**0.24**	**0.021**
Spouse die[b]	-0.43	0.23	0.083
Spouse ill[b]	**-0.68**	**0.12**	**<.0001**

[1]Unweighted scale, higher score indicates more stressful life events (range: 0-11).

[2]Weighted Scale, higher score indicates more stressful life events (range: 0-33).

[a]Respondents who had < 3 stressful life events at all time periods were the reference; [b] "No" responders were the reference.

[†]Only variables that were significant in the previous model were included in the final model.

Note. Social support variables included social support and social strain; comorbidities included diabetes, depression, and cardiovascular disease.

SES covariates include year, ethnicity/race, education, income, cohabitation status, alcoholic intake per week, smoking, marital status, and caregiving responsibilities.

Comorbidity covariates include BMI (as a continuous variable), cardiovascular disease, diabetes, depression, and blood pressure.

CHAPTER 3: Examining the association between physical activity and cognition

Background

Cognitive function

Subtle decrements in cognitive function (i.e., cognitive impairment) is a prevalent geriatric syndrome that may ultimately lead to a loss of independent function and disability (American Psychiatric Association, 2006). Cognitive impairment may accurately predict future dementia and may be considered a marker of preclinical disease (Kawas et al., 2003).

While brain deterioration and cognitive decline are considered common characteristics of aging, not everyone experiences decline at the same rate and/or to the same degree. Specifically, data suggest women may be two to three times more likely than men to develop Alzheimer's disease (Birge, 1996).

These individual differences in aged persons suggest that deterioration and decay is not an inevitable product of aging. Thus, research on factors that may protect against diminished cognitive function in aged adults is of critical public health importance, especially considering the number of individuals $\geq$ 65 years is set to dramatically increase as the baby boom generation ages (US Bureau of the Census, 1996).

Physical Activity

Accumulating evidence indicates regular physical activity can attenuate the aforementioned physiologic effects of age-related decline in cognitive function. For

instance, several prospective cohort studies have reported that people who are physically active are less likely than sedentary persons to experience cognitive decline and dementia in later life (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Weuve et al., 2004; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001). These effects have been shown to be greatest in higher order cognitive processes that are mediated by the hippocampus, such as working memory (Colcombe & Kramer, 2003).

Few large prospective cohort studies that include female participants have highlighted the protective role of regular physical activity in lowering the risk of cognitive function decline (Weuve et al., 2004) and dementia. Weuve et al (2004) reported that women in the highest quintile of physical activity, compared to women in the lowest quintile, had 20% lower odds of cognitive impairment. Similarly, Laurin et al. (2001) found that women with the highest physical activity level had 42% and 37% lower odds of Alzheimer's Disease and dementia, respectively.

To study specific mechanisms, most studies are limited to animal subjects, because of the cost and burden of conducting extensive MRIs on large numbers of people. However, even the randomized controlled trials in this area have sample sizes of < 100 participants. Therefore, it is not surprising that studies have reported little to no effect given the less than desirable levels of power. In addition, operationalization of physical activity differs among studies, thus accurate comparison of studies is unattainable. While most studies have used questionnaires to estimate PA, virtually every study employed a different scale to assess PA and consequently used different categories or levels of PA. Also, applying results of studies conducted with animal

subjects to the human population may not be pragmatic because animals are able to be sacrificed in order to measure organ sizes, such as the hippocampus. Prospective studies using human subjects are mainly limited to using proxy measures of cognitive function decline, such as verbal and written tests, instead of objective measures such as hippocampal size.

While these results provide evidence of a basis for the protective role of regular physical activity in maintaining and enhancing cognitive functioning in older adults, no study has included a diverse sample of elderly women. Further, previous studies have not controlled for an inclusive set of physical (e.g., BMI, blood pressure, comorbidities) and emotional (e.g., social support) confounders. Consequently, there seems to be a need for evidence that can detail the amount of physical activity that is warranted to produce beneficial results against cognitive function decline.

Purpose

The purpose of this study is to examine the prospective relationship between physical activity and cognitive function. The purpose of the study were addressed through answering the following research questions and hypotheses:

Manuscript 2: Research questions and hypotheses
R3: What is the prospective association between physical activity and cognitive function?
H3: Physical activity will be positively related to cognitive function. Specifically, individuals with higher levels of physical activity will have higher cognitive

functioning scores, compared to those with low levels of physical activity.
R4: Does meeting public health physical activity guidelines protect against cognitive function decline? **H4**: Those who do not meet public health physical activity guidelines will have lower cognitive function scores compared to those who do meet guidelines.

Methods

Theoretical Framework

The theoretical framework used to inform this investigation is based on the risk and protective factors of the stress process theory. This theory mainly explains the psychopathology of health outcomes in terms of exposure to stress and ameliorative factors, such as physical activity. This theory identifies three sources (social, psychological, and physiological environments) as major contributing factors in the life stress process. However, this manuscript will focus on physical activity, which is considered a social factor.

Design

Data from the Women's Health Initiative Memory Study (WHIMS; *n* = 7,479), a subset of participants randomly selected from the WHI Hormone Therapy Trial (WHI HT), was used to address all specific questions. The WHI is a large, multicenter investigation of postmenopausal women enrolled in one of the 3 randomized clinical trials (Hormone Therapy, Diet Modification or Calcium Vitamin D) or the Observational Study. The WHI was initiated in 1992 and enrolled participants at one of 40 WHI clinical centers nationwide. Participants were followed annually up to 8.5 years (*M* = 5.2 yrs). The WHI HT was stopped early due to the unfavorable risk-to-benefit ratio and evidence of early harm (Writing Group for the Women's Health Initiative Investigators, 2002). The decision to stop the WHI HT also ended WHIMS.

WHIMS is a double-masked, placebo-controlled, clinical trial. Thirty-nine of the WHI clinical centers and 10 satellites participated in WHIMS. Participants in the WHIMS,

an ancillary study to the WHI HT, were recruited between May 1996 and December 1999 from women in the WHI HT. A total of 7,480 women ages 65-79 were recruited from the WHI HT. Of the 7,480 women, 2,948 are in the estrogen only (E-alone) study for women without a uterus at the time they enrolled and 4,532 are in the estrogen plus progestin (E+P) study for women with a uterus at time of enrollment. Participants were followed annually up to 8 years (*M* = 4.5 yrs).

To control for the possible effects of the intervention drug on the outcome, only participants randomized in the placebo groups were included for all analyses (*n* = 3775). In addition, we only used data from 5 data collection points (baseline and follow-up years 1 through 4) due to the significant loss to follow-up after year 4.

Participants

To address all research questions, complete data on healthy women aged 65-79 years enrolled the WHI HT and the WHIMS are available. Of these combined cohorts, complete data are available for approximately *n* = 3775 healthy women who did not receive an active treatment.

Key exclusion criteria for participation in the WHI HT were the following: invasive cancer within the previous 10 years, major cardiovascular (myocardial infarction or stroke) disease events in the previous 6 months, medical conditions contraindicating for hormone therapy, systolic blood pressure > 200mmHg or diastolic blood pressure > 105mmHg. Key inclusion criteria for participation in the WHIMS were being 65 years or above and free of dementia. The Modified Mini-Mental Exam (3MSE) was used as a primary screening assessment of cognitive functioning (Teng & Chui, 1987) at baseline

screening and then at annual follow-up visits. Those who scored below a set cutpoint, which were based on previous studies (Graham & Rockwood, 1997; Tombaugh et al., 1996), were scheduled for a more extensive neurocognitive assessment and neuropsychiatric examination.

Measures

All of the measures in this application have already been assessed on the WHI HT and WHIMS cohorts and are available through the public use data sets.

Dependent variable

Cognitive function

Global cognitive function was based on scores from the 3MSE collected at baseline and annually for up to 8 years. The 3MSE consists of 15 items that produce a range of possible scores from 0-100, with higher scores reflecting better cognitive functioning. The 3MSE, a quantitative indicator of cognitive function widely used clinically and epidemiologically, has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia (Bravo & Herbert, 1997; McDowell et al., 1997). A score of < 88 on the 3MSE has been suggested as the optimal cutpoint to classify this sample of women (with education levels $\geq$ 9 years) with probable dementia or composite mild cognitive impairment/probable dementia, and a score of < 80 for those with < 9 years of education. Trained and certified technicians, who administered the 3MSE in the WHIMS, were masked to the treatment assignment of all participants.

Independent variable

Physical activity

Physical activity behavior was measured using self-report procedures. Participants estimated the frequency and duration of walking and of several other types of activities that ranged in intensities (e.g., mild, moderate, and strenuous). To assess mild activities, a series of questions asked about walks outside the home for more than 10 minutes without stopping, average duration of each walk, and usual walking pace. Slow dancing, bowling, and golf were also considered mild activities. Moderate exercise was defined as activities that are "not exhausting", such as biking outdoors, using an exercise machine (e.g., stationary bicycle or a treadmill), calisthenics, easy swimming, and popular or folk dancing. Vigorous exercise was defined as activities during which "you work up a sweat and your heart beats fast," including aerobics, aerobic dancing, jogging, tennis, and swimming laps. Weekly energy expenditure scores were converted to metabolic equivalents (MET score), using a standardized classification of the energy expenditure associated with physical activities.

We decided to operationalize physical activity according to federal physical activity guidelines. Federal guidelines recommend that older adults, aged 65 years and older, should follow guidelines for adults, which are as follows: 150 minutes per week of moderate to vigorous intensity physical activity, or 75 minutes per week of vigorous intensity physical activity. To help elucidate at which physical activity or energy expenditure level an individual should achieve in order to garner the most benefit, four physical activity variables were created: total MET-hours per week, total time spent in

moderate to vigorous physical activity per week, total time per week spent walking per week, and total time spent in vigorous physical activity per week. Considering the characteristics of our sample, we decided to use a walking physical activity variable because it is an attainable and prevalent form of physical activity for older women.

The physical activity assessment questionnaire was found to have adequate reliability (weighted kappas among all women ranged from 0.67 to 0.71) (Langer, White, Lewis, & et al., in press).

Covariates

Sociodemographics

Age, *race/ethnicity*, *education and insurance status* were assessed via self-report questionnaires. Women self-identified as non-Hispanic white, black or African American, Hispanic or Latino, Asian/Pacific Islander, American Indian or Alaska Native, or other. Participants indicated one of 11 categories of educational attainment: Didn't go to school, Grade school (1-4 years), Grade school (5-8 years), Some high school (9-11 years), High school diploma or GED, Vocational or training school, Some college or Associate Degree, College graduate or Baccalaureate Degree, Some post-graduate or professional, Master's Degree, or Doctoral Degree.

Behavioral factors

*Smoking***.** Participants indicated number of cigarettes usually smoked each day. *Smoking history*. If participants indicated they were ever a regular smoker, they were asked how many years they were a regular smoker. Participants also indicated the number of years they lived with a smoker as a child. *Alcohol consumption*. Alcohol

consumption was determined from responses to a single two-part item. The first part categorized alcohol intake on a weekly/monthly level; the second part asked participants to indicate number of servings per week of beer, wine and/or liquor based on a medium serving size which is 12oz of beer, 6oz of wine and 1½ oz of liquor.

Antidepressant Use. To measure antidepressant use, participants were asked to bring all current medications to baseline interviews (WHI Clinical Coordinating Center).

Comorbid conditions and physical factors

Diabetes. Participants self-reported if a physician had ever told them that they had "sugar diabetes" when they were not pregnant. Family history of diabetes was also be ascertained. *Body mass index (BMI).* BMI was measured by trained research personnel and calculated from height and body weight as follows: BMI (kg/m^2) = Body weight (kg) / Height $(m)^2$ and was used to classify subjects as normal weight, at risk for overweight or overweight using the cutpoints as recommended by the U.S. Centers for Disease Control and Prevention Centers for Disease Control and Prevention.

Cardiovascular disease. Family history of cardiovascular disease was also ascertained.

Depression. Depressive symptoms were measured using the 6-item scale from the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977). The CES-D has shown good criterion validity among older adults with a weighted sensitivity of 100% and specificity of 88% (Beekman et al., 1997).

Unfortunately, data are not available on family history of dementia and apolipoprotein E4 levels of WHIMS participants. Thus, it was not possible to test for a

possible interaction between these factors and physical activity on cognitive function decline.

Analysis

To address R3 and R4, a linear mixed effects model, which combine fixed-effects regression methods (placebo group and covariates) and a generalization of the variance components (site-level factors and time), was applied.

Since physical activity data were also collected at several time points, individual rates of change for each participant were obtained. To this effect, mixed effects linear models were fit with physical activity as a function of time (for each data collection point), with a random participant-specific intercept and slope added to the model. All informative slopes (i.e., statistically significant) were used in analyses as estimates of rates of stressful life events.

Covariates for the mixed models included race/ethnicity, age, year of data collection, SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease. Individual-level factors (e.g., SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease) were treated as fixed effects, and site-level factors and time were treated as random effects.

Linear mixed models

Linear mixed effects models were run using SAS PROC MIXED, which supports mixed effects models.

R3: What is the prospective association between physical activity and cognitive function?

H3: Physical activity will be positively related to cognitive function. Specifically, individuals exposed to lower levels of physical activity will have lower cognitive function scores, compared to those with high levels of physical activity.

R4: Does meeting public health physical activity guidelines protect against cognitive function decline?

H4: Those who do not meet public health physical activity guidelines will have lower cognitive function scores compared to those who do meet guidelines.

Let CF_{ij} denote the incidence of cognitive function (CF) decline for observation *i* at time *j* at site *k*, the linear mixed model can be written:

$$CF_{ijk} = \alpha + \beta_1 * PA_{ijk} + \beta_2 * time_{ik} + \beta_3 * \text{covariate}_{ijk} + \gamma_{i0} + \gamma_{i1} * time_{ik} + \gamma_{i2} * site_{ik} + \varepsilon_{ijk}$$

Where $\gamma_{i0} \sim N\left(0, \sigma^2_{\text{int}ercept}\right), \gamma_{i1} \sim N\left(0, \sigma^2_{time}\right), \gamma_{i2} \sim N\left(0, \sigma^2_{site}\right).$

Note. PA: physical activity.

Results

The average follow-up for participants enrolled in the estrogen-alone trial was 5.4 years and 4.06 years for those in the estrogen plus progestin trial. Due to significant loss to follow-up, we only included data up to and including data collection period year 4. Table 2.1 provides a list of variables and the respective assessment instrument. Tables 2.2 and 2.3 provide sample characteristics by quintiles of total MET-hours per week and year, respectively. The average age at baseline for this combined sample was 70.1 (*SD* $\pm$ 3.85) years. The most often reported income was $20,000 to $34,999 (30%) and 53% of the sample were married or in a marriage-like relationship. Based on BMI, 29% of this sample had a BMI within the normal range (i.e., BMI = <25) while 35.9% were overweight (BMI = 25-29.9) and 34.4% were obese (BMI $\geq$ 30; data not shown). Approximately 66% of the sample had at least some college education. In addition, 53% of the women never smoked cigarettes and 63% did not provide informal care for an ill friend or spouse.

On average, the women in this sample did not meet the recommended levels of 150 minutes per week in moderate to vigorous physical activity, with a sample average of 92.8 minutes per week. In addition, the means for time spent in moderate to vigorous physical activity did not precipitously decrease over time. At baseline, women on average reported spending 89 minutes in moderate to vigorous physical activity per week, and reported spending 82 minutes in moderate to vigorous physical activity per week at 4-years follow-up. This decline was not statistically significant.

Longitudinal associations between physical activity and cognitive function

Table 2.4 displays results of several multivariate, mixed effects models that examined the prospective association between quintiles of four measures of physical activity and cognitive function. Results from the age-adjusted only model using total MET score (first column) indicate that those in the lower quintile category, quintiles 1 – 3, have significantly lower cognitive function scores compared to those in the highest MET score quintile ($p < 0.001$). However, this relationship is no longer significant in the fully adjusted model. Data in the second column appear to indicate that cognitive function scores are not significantly different by walking expenditure quintiles in all models.

For time spent in vigorous physical activity (column three), those in the two lowest quintiles had significantly lower cognitive functions scores compared to those with in the highest quintile of moderate to vigorous physical activity per week ($p = 0.002$). This statistically significant relationship does not remain when SES covariates and comorbidities are included in the model. Column four results seem to indicate that moderate to vigorous physical activity is only significantly associated with cognitive function scores in an age-adjusted only model. However, after adjusting for SES and comorbidity variables, there are not any statistically significant differences between any quintile. However, the trend for all models using time spent in moderate to vigorous physical activity as the exposure is significant, indicating that as time spent in moderate to vigorous physical activity increases, so does cognition scores.

Table 2.5 displays results of the mixed effects analysis when the physical activity variables are dichotomized based on federal guidelines for physical activity. The federal guidelines for the three physical activity categories are: MET-hours per week (<8.33 or ≥8.33 MET-hrs/wk), time spent in vigorous physical activity per week (<75 or ≥75 min/wk), and time spent in moderate to vigorous physical activity per week (<150 or ≥150 min/wk). In the age-adjusted model only, all physical activity variables are statistically significant. For instance, those meeting recommended guidelines for time spent in moderate to vigorous physical activity per week, vigorous physical activity per week, and total MET score per week have on average higher cognition scores by 0.22, 0.32, and 0.27, respectively, of a point compared to those not meeting recommendations.

After adjusting for SES variables, these relationships remain significant for two of the physical activity variables: time spent in vigorous physical activity and total MET score per week. Specifically, those who meet recommendations for total MET score have on average 0.13 of a point higher on the 3MSE compared to those who do not meet recommendations ($p = 0.038$). For those who meet recommendations for time spent in vigorous physical activity have on average 0.19 of a point higher on the 3MSE compared to those who do not meet recommendations ($p = 0.042$).

After fully adjusting for many confounding factors, only one physical activity variable remains significant. There is a marginally significant association, such that those who do not meet guidelines based on MET-hours per week on average scored

0.17 points lower on the 3MSE compared to those who meet US physical activity guidelines (p = 0.065).

Discussion

The primary purpose of this study was to examine the longitudinal relationship between several physical activity measures and cognitive function. We first aimed to identify the level at which physical activity is associated with lower cognitive function scores. For our first hypothesis, we predicted that physical activity will be positively related to cognitive function. Our data from an ethnically diverse sample of postmenopausal women suggest that those who do not engage in any level of physical activity have lower cognitive function scores compared to women who engage in regular physical activity. However, it should be noted that the mean cognition scores for this sample slightly increased over time, indicating that our sample of post menopausal women were highly educated and high functioning. Hence, these results may not be generalizable to a lower functioning group of women with lower educational attainment.

Our results appear to lend support to current federal guidelines that encourage adults to achieve at least 500 MET-minutes or 8.33 MET-hours per week of aerobic activity. Women who did not achieve at least 500 MET-minutes per week appeared to have lower cognitive function scores compared to those who met guidelines, after controlling for several behavioral and physical confounding factors. These results are consistent with previous findings (Laurin et al., 2001; Weuve et al., 2004) that suggest those who do not engage in any physical activity are at higher risk for cognitive function decline compared to those who engage in some physical activity. It should be noted

that these results were detected in spite of our sample not showing a significant decline in cognitive function, as evidenced by the 3MSE scores.

Biologic Plausibility of physical activity and Cognitive Function

There are several plausible mechanisms through which physical activity may reduce the age-related effects of cognitive decline. Animal studies have shown that chronic aerobic exercise can lead to increases in growth factors such as brain-derived neurotrophic factor (Cotman & Berchtold, 2002) and increased cell production in the hippocampus (van Praag, Christie, Sejnowski, & Gage, 1999). In turn, these growth factors may initiate structural changes, such as the growth of new capillaries in the brain (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990) and an increase the length and number of the dendritic interconnections between neurons (Cotman & Berchtold, 2002). The end result is a better interconnected brain that is more plastic and adaptive to change, ultimately slowing cognitive decline (van Praag et al., 1999). Human studies are just beginning to corroborate what was previously found in animal studies (Colcombe & Kramer, 2003). For instance, a study using magnetic resonance imaging found that older adults with a lifelong history of aerobic exercise had better structural preservation in the brain than did age-matched sedentary counterparts (Colcombe & Kramer, 2003). Another study reported that increased cardiovascular fitness can affect improvements in the plasticity of the aging human brain (Colcombe et al., 2004).

What this study adds

Physical activity may be an important mechanism that buffers against age-related effects of cognitive function decline. However, the possible ameliorating role of

physical activity against cognitive function decline has not been fully examined among post-menopausal women. Finding low-cost behaviors that lower risk of cognitive decline is critical for the successful implementation of public health interventions that have the potential of affecting a high proportion of the US female population.

Strengths and limitations

There were several strengths of this study. We used a nationally representative sample of post-menopausal women who were enrolled in the largest randomized clinical trial of hormone replacement therapy. In order to eliminate effects of any intervention, only participants randomized into the placebo arms were used. Due to the relatively large sample size and multiple follow-up points, we were able to use mixed effects modeling, a statistical analysis that incorporated all data points (up to 4 years) for both the exposure and outcome variables. Unlike similar previous studies, we were also able to include adjust for many confounders, such as social support, comorbidities, physical markers (e.g., BMI, blood pressure), and behavioral variables (e.g., smoking, alcohol drinking).

In spite of the study strengths, several limitations need to be acknowledged. The use of a self-report assessment of physical activity may not accurately reflect an individual's level of physical activity. It has been widely reported that accurate estimation of physical activity through self-report measures are highly suspect to under- and overestimations. Hence it is quite possible that our results were affected by random misclassification bias, biasing our results toward the null hypothesis. Further, our sample appeared to be a well-educated, highly functioning group. As such, there

was not much variance regarding cognitive function scores. Hence, our results may not be applicable to the general population.

The secondary nature of data analyses are limited to what was collected during the data collection points. Consequently, operationalization of all measures was based on decisions made by WHI investigators. Assessment of all variables involved in addressing our specific research questions may not be ideal and not all possible confounding variables may be available. The most notable is not being able to control for the APO e4 allelle.

In addition, certain biases may have been introduced due to the prospective nature of the clinical trials. Specifically regarding recruitment and enrollment of minority women, data were not collected on the total number of women contacted or on women who chose not to make the initial contact. Therefore, it is impossible to discern differences between racial/ethnic groups with regard to willingness to participate in the WHI trials. While our sample appeared to be a highly functioning, well educated group, nonetheless our results indicate that repeated exposure to certain life events may pose a risk in the maintenance of cognitive function skills.

Conclusion

Considering the number of individuals $\geq$ 65 years is set to dramatically increase as the baby boom generation ages and the prevalence of Alzheimer's disease is expected to double by 2025 and nearly triple by 2050,(Hebert et al., 2003) elucidating protective factors for cognitive function decline become imperative. Our results appear to lend support that any amount of physical activity compared to none is beneficial to

sustaining cognitive functioning over time among a representative sample of post-menopausal women.

Results Tables

Table 2.1. Study Variables and Instruments

Variable	Instrument
Independent Variable	
Stressful life events	Questionnaire
Covariates	
Sociodemographics	Questionnaire
Psychosocial	
Depression	CES-D
Social support	MOS
Behavioral	
Smoking	Questionnaire
Alcohol consumption	Questionnaire
Medical	
Cardiovascular disease	Questionnaire
Diabetes	Questionnaire
BMI	Questionnaire
Dependent Variable	
Cognitive function	3MSE

Table 2.2. Variables of interest by data collection period.

	Baseline	Year 1	Year 2	Year 3	Year 4
Mean Cognitive function	95.2 (4.3)	95.9 (4.0)	96.3 (4.1)	96.5 (3.9)	96.6 (4.3)
Mean MET-hours per week (SD)	11.9 (14.3)	11.3 (13.3)	10.9 (13.2)	11.0 (13.4)	11.1 (13.4)
Mean MET-hours per week from walking (SD)	4.2 (5.7)	3.9 (5.5)	3.5 (5.2)	3.6 (5.2)	3.6 (5.2)
Mean minutes of MVPA per week (SD)	89.2 (142.3)	83.9 (129.1)	79.8 (128.9)	81.2 (130.7)	82.2 (130.7)
Mean minutes of VPA per week (SD)	27.8 (68.2)	25.9 (63.7)	25.1 (62.2)	25.4 (62.5)	25.3 (61.9)
Mean Age (SD)	70.1 (3.8)				

Table 2.3. Sample characteristics by physical activity category.

Variable	Total	Quintile of Total MET-hours per week				
		1 (lowest)	2	3	4	5 (highest)
Dependent variable						
Mean cognitive function score (SD)	96.3 (4.07)	95.7 (4.47)	96.0 (4.24)	95.9 (4.39)	96. 4 (3.71)	96.5 (3.81)
Independent variables						
Mean MET-hours per week (SD)	12.9 (13.64)	0.0 (0.00)	2.2 (1.10)	6.9 (1.69)	14.2 (2.62)	32.9 (14.31)
Mean MET-hours per week from walking (SD)	5.0 (5.75)	0.0 (0.00)	1.4 (1.31)	3.3 (2.89)	5.3 (4.98)	8.8 (7.90)
Mean minutes of MVPA per week (SD)	92.8 (134.66)	0.0 (0.00)	6.4 (11.53)	37.3 (40.95)	99.4 (72.30)	273.3 (171.73)
Mean minutes of VPA per week (SD)	28.4 (65.12)	0.0 (0.00)	0.8 (3.93)	5.1 (13.86)	22.6 (39.94)	100.8 (105.82)
Mean age (years, (SD))	70.1 (3.85)	70.2 (3.94)	70.1 (3.91)	70.2 (3.85)	70.0 (3.82)	69.9 (3.74)
Mean BMI (kg/m^2,(SD))	27.9 (5.24)	30.3 (6.22)	29.4 (5.62)	28.2 (5.42)	27.7 (5.14)	27.0 (4.88)
Mean systolic blood pressure (SD)	129.4 (16.83)	131.7 (17.59)	131.0 (17.62)	129.6 (17.20)	129.8 (16.90)	129.0 (17.21)
Mean diastolic blood pressure (SD)	73.4 (9.15)	73.7 (9.66)	73.3 (9.72)	73.0 (9.46)	72.9 (9.26)	73.5 (9.17)

Table 2.3 (cont.). Sample characteristics by physical activity category.

Variable	Total	Quintile of Total MET-hours per week				
		1 (lowest)	2	3	4	5 (highest)
Ethnic/Race (%)						
American Indian or Alaskan Native	0.4	0.1	0.1	0.1	0.0	0.1
Asian or Pacific Islander	1.6	0.2	0.3	0.2	0.3	0.5
Black or African-American	7.2	1.8	1.7	1.2	1.1	1.0
Hispanic/Latino	2.3	0.4	0.4	0.6	0.4	0.5
White (not of Hispanic origin)	87.2	16.6	17.9	17.6	17.8	17.8
Other	1.4	0.3	0.3	0.4	0.3	0.3
Level of Education (%)						
< High school	26.2	5.0	5.3	5.0	5.2	5.8
High school diploma or GED	7.4	2.1	1.8	1.46	1.08	0.9
< 4 years college	35.2	7.6	8.1	7.5	6.6	5.6
≥ 4 years college	31.1	4.6	5.5	6.1	7.1	7.9
Income (%)						
< $19,999	27.0	6.5	6.3	5.7	4.5	4.0
$20,000 to $34,999	29.9	5.9	6.7	6.2	5.7	5.4
$35,000 to $49,999	20.0	3.6	4.0	3.9	4.4	4.1
≥ $50,000	23.1	3.2	3.8	4.2	5.4	6.5
Marital status (%)						
Never married	3. 6	2.4	2.6	2.3	2.2	2.2
Divorced or separated	12.2	0.7	0.8	0.7	0.6	0.7
Widowed	30.4	10.2	10.9	10.6	11.0	11.5
Presently married/marriage-like	52.9	6.1	6.3	6.4	6.1	5.7

Table 2.3 (cont.). Sample characteristics by physical activity category.

Variable	Total	Quintile of Total MET-hours per week				
		1 (lowest)	2	3	4	5 (highest)
Living alone						
No	60.1	12.3	13.0	12.0	12.2	12.1
Yes	39.9	7.0	7.7	8.0	7.8	7.9
Smoking status (%)						
Never Smoked	52.9	9.0	10.8	11.0	10.7	11.0
Past Smoker	7.2	7.0	8.1	7.6	8.8	8.6
Current Smoker	39.9	1.7	2.0	1.6	1.2	0.7
Number of times per week a participant currently helps a friend or family member						
No	63.4	12.2	13.2	12.8	12.2	12.1
Less than once a week	7. 5	1.5	1.4	1.4	1.7	2.1
1-2 times a week	13.5	2.5	2.9	2.8	3.0	3.03
3-4 times a week	4.3	0.8	1.0	0.9	1.0	0.9
5 or more times a week	11.4	2.2	2.2	2.1	2.0	2.1

MVPA = Moderate to vigorous physical activity; VPA = vigorous physical activity.

Table 2.4. Results of longitudinal mixed effects analysis examining the prospective relationship between quintiles of physical activity measures and cognitive function.

	Total MET score (MET-min/wk)		Walking expenditure (MET-hr/wk)		Time spent in vigorous activity (Min/wk)		Time spent in MVPA (Min/wk)	
Variable	β	SE	β	SE	β	SE	β	SE
Model 1: Age-Adjusted								
Quintile 1 (lowest)[a]	**-0.51******	0.12	-0.04	0.12	**-0.46****	0.15	**-0.52******	0.12
Quintile 2	**-0.46*****	0.12	-0.16	0.15	**-0.66****	0.20	-0.29	0.22
Quintile 3	**-0.38****	0.12	-0.06	0.14	-0.29	0.20	**-0.37****	0.13
Quintile 4	-0.16	0.11	0.06	0.12	-0.08	0.19	0.02	0.11
P-value for physical activity in model	**0.0002**		0.509		**0.002**		**<0.0001**	
Model 2: Model 1 + SES								
Quintile 1 (lowest)[a]	-0.18	0.13	0.14	0.12	-0.24	0.15	-0.20	0.11
Quintile 2	-0.18	0.12	0.03	0.14	-0.39	0.20	0.01	0.22
Quintile 3	**-0.20***	0.12	0.14	0.13	-0.12	0.20	-0.05	0.13
Quintile 4	-0.06	0.11	0.13	0.11	-0.12	0.19	0.15	0.11
P-value for physical activity in model	0.222		0.667		0.177		**0.009**	
Model 3 (Full Model): Model 1 + Model 2 + Comorbidities								
Quintile 1 (lowest)[a]	-0.15	0.13	0.17	0.12	-0.14	0.15	-0.18	0.11
Quintile 2	-0.15	0.12	0.07	0.15	-0.31	0.20	-0.01	0.22
Quintile 3	-0.10	0.12	0.16	0.13	-0.04	0.20	-0.02	0.13
Quintile 4	-0.03	0.11	0.14	0.12	0.01	0.19	-0.02	0.12
P-value for physical activity in model	0.684		0.609		0.434		**0.011**	

MVPA = Moderate to vigorous physical activity. [a]Quintile 5 (highest) was the reference.

SES covariates include year, ethnicity/race, education, income, cohabitation status, alcoholic intake per week, smoking, marital status, and caregiving responsibilities.

Comorbidity covariates include BMI (as a continuous variable), cardiovascular disease, diabetes, depression, and blood pressure.

$p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$; $^{\wedge}p = 0.055$; $^{\#}p = 0.06$.

Table 2.5. Results of longitudinal mixed effects analysis examining the prospective relationship between recommendations of physical activity levels and cognitive function.

	Total MET score based on guidelines (MET-hr/wk)[†]			Time spent in MVPA based on guidelines (Min/wk) [*]			Time spent in vigorous activity based on guidelines (Min/wk)[^]		
Variable	β	SE	*p* - value	β	SE	*p* - value	β	SE	*p* - value
Model 1: Age-Adjusted [a]	**-0.27**	0.07	**<0.0001**	**-0.22**	0.08	**0.004**	**-0.32**	0.09	**0.001**
Model 2: Model 1 + SES [a]	**-0.13**	0.06	**0.038**	-0.06	0.07	0.388	**-0.19**	0.09	**0.042**
Model 3 (Full Model): Model 1 + Model 2 + Comorbidities[a]	-0.12	0.07	0.064	-0.05	0.07	0.467	-0.17	0.09	0.065

MVPA = Moderate to vigorous physical activity.

[a] Those meeting recommendations were reference category for all models.

[†]Scores were categorized based on meeting ≥ 500 MET-minutes per week or ≥ 8.33 MET-hours per week.

[*]Scores were categorized based on meeting 150 minutes of moderate to vigorous physical activity per week.

[^] Scores were categorized based on meeting 75 minutes of vigorous physical activity per week.

SES covariates include year, ethnicity/race, education, income, cohabitation status, alcoholic intake per week, smoking, marital status, and caregiving responsibilities.

Comorbidity covariates include BMI (as a continuous variable), cardiovascular disease, diabetes, depression, and blood pressure.

CHAPTER 4: Examining the pathways through which stressful life events influence cognition

Background

Stressful life events

Major life events are considered a measure of life stressors (Rahe, 1979). Major life event stressors are characterized by potentially high-impacting events, such as the loss of a spouse or relocation. One purpose of measuring life events is to establish a temporal sequence between an increase in the number of life events and the onset of illness or disease. The role that stressful life events play in the etiology of various diseases has been researched for the last three decades (Rabkin & Struening, 1976). It is hypothesized that excessive stress may play a role in the pathogenesis of chronic diseases (Dodge & Martin, 1970; Greenwood et al., 1996a; McEwen, 2004). The underlying assumption is that the negative nature of events is not the important factor, but the amount of change that is required to readjust to a tolerable level of functioning.

Disease onset is generally thought to be influenced by a complex interaction of multiple factors, including the presence of stressful environmental conditions, perception by the individual that such conditions are stressful, the relative ability to cope with or adapt to these conditions, and a genetic predisposition to a disease as well as carrying risk factors for a given disease (Rabkin & Struening, 1976). The potential negative effects of stress may likely be the result of at least three characteristics of the stressor: magnitude, intensity, and duration (McEwen, 1998). In its acute form, stress is a necessary adaptive mechanism for survival. However, repeated occurrences of acute

stressors may cause overactivation and dysregulation of the stress regulatory systems, which in turn, may produce negative effects on brain morphology and chemistry (McEwen, 2008). Stress-induced changes and remodeling of the brain have been associated with various health outcomes, including Alzheimer's disease (Srivareerat et al., 2009). In this context the stress concept may greatly aid in explaining why some individuals are more susceptible to illness than others.

In cross-sectional and prospective investigations, modest but statistically significant relationships have been found between higher number of life events and increased risk of disease (Kop, 1997; Pyykkönen et al.; Vitaliano et al., 2002; von Kanel et al., 2003), depression (Kessler, 1997), and physical impairment (Whitehead et al., 1992). However, very few studies have examined the association between stressful life events and cognitive functioning and only one study has prospectively examined the association between life events and declines in memory (Peavy et al., 2009).

Psychosocial factors and social support

Women may rely on various internal and external resources as a way to cope with negative stressors or life events. The most prevalent internal resources used that have been studied in the literature include optimism (Carver et al., 1993; Epping-Jordan et al., 1999), hostility, expression of negative emotion (King & Emmons, 1990), and ambivalence over the expression of emotions (King & Emmons, 1990). The commonly reported indicator of external resources used to cope with negative stressors is social support (Ashing-Giwa, 1999; Cohen & Syme, 1985; Glanz & Lerman, 1992; Israel & Schurman, 1990).

Optimism is defined as a stable personality trait characterized by the general expectancy that future events will be relatively positive (Scheier & Carver, 1992). In general, optimism is associated with a multitude of positive health benefits, including better quality of life, better health outcomes, and lower diastolic blood pressure reactivity in stressful situations (Andersson, 1996; King, Rowe, Kimble, & Zerwic, 1998; Miller, Manne, Taylor, Keates, & Dougherty, 1996; Sheppard, Maroto, & Pbert, 1996; Sumi, 1997).

It is suggested that when individuals are ambivalent or in conflict over their expression of emotion, negative health outcomes occur (King & Emmons, 1990). One aspect of the Womens' Health Initiative Study was to examine two personality traits with hypothesized links to women's health: expression of negative emotion and ambivalence over the expression of emotions (King & Emmons, 1990). Ambivalence over the expression of emotions is defined as a level of comfort with an individual's particular style of emotional expression (Michael et al., 2005). Ambivalence is commonly described as a disposition or trait phenomenon and has been positively correlated with self-reported measures of physical symptoms and psychological distress (King & Emmons, 1990).

Expression of negative emotion, the degree to which a person expresses or inhibits emotional expression, especially the inhibition of negative emotion has been examined in association with several chronic illnesses, as well as health-related behaviors (Smyth, Stone, Hurewitz,& Kaell, 1999; Stanton et al., 2000). In other words, it is thought that expressing negative emotions, such as anger, sadness, or fear, is good

for psychological and physical health outcomes. Specifically, it is generally accepted as normal and healthy for an individual to experience a period of intense mourning after the loss of a loved person. The ability to express negative emotions instead of ambivalence has been positively related to a greater psychosocial risk profile, including an increased risk for depression, having a less positive outlook; and reporting more stressful life events, greater social strain and less social support (Michael et al., 2006).

A considerable body of evidence supports an association between cynical hostility (Cook & Medley, 1954) and an increased risk of negative health outcomes, such as coronary heart disease. Cynical hostility, defined as "a set of negative attitudes, beliefs, and appraisals concerning others…a belief that others are generally unworthy and not to be trusted" (Smith, 1992, p. 139), has been described as an internal risk factor (Kline, Fekete, & Sears, 2008). It is thought that more hostile individuals experience a more taxing interpersonal environment (Kline et al., 2008). Recent research has found that individuals with high hostility compared to low hostility appraised videotapes depicting ambiguous social interactions as less friendly and less socially supportive (Vranceanu, Gallo, & Bogart, 2006).

Social support is a complicated construct involving between persons and within-person dynamics among the identified person and one or more family members or friends. Evidence suggests that social network resources and informal social supports may enable people to cope with stress (Coyne & Downey, 1991). It is thought that individuals who are integrated into formal or informal social networks are more likely to experience a more supportive environment during major life stressors, and are

consequently better equipped to cope with stressful events. There are a number of studies examining the positive functions of social resources in the association between life's stressors and adaptation. For instance, research has provided support that the experience of stress, coupled with low levels of social support, is associated with many health outcomes, such as psychological distress (August, Rook, & Newsom, 2007), cardiovascular disease (Greenwood, Muir, Packham, & Madeley, 1996b; Tennant, 1999).

Accumulating evidence indicates that regular physical activity can attenuate the physiologic effects of age-related decline in cognitive function. Few large prospective cohort studies that include female participants have highlighted the protective role of regular physical activity in lowering the risk of cognitive function decline (Weuve et al., 2004) and dementia. Weuve et al (2004) reported that women in the highest quintile of physical activity, compared to women in the lowest quintile, had 20% lower odds of cognitive impairment. Similarly, Laurin et al. (2001) found that women with the highest physical activity level had 42% and 37% lower odds of Alzheimer's disease and dementia, respectively.

It is reasonable to extend a model toward a health outcome such as cognition, given the negative association between stress and cognition and the protective effects of internal and external resources on health outcomes. Within the context of a model of risk factors versus protective factors, we propose that stressful life events is the exposure or risk factor whereas psychosocial factors, social support, and physical activity are the protective factors. Relative to the stress-cognition relationship, we propose that internal and external resources may act as mediators and physical activity

may act as a moderator. Specifically, individuals who are: more optimistic, less hostile, less ambivalent, and better at expressing negative emotions are less likely to view and react to negative life events in a manner that taxes the stress regulatory systems. Since it is less likely that stressful life events is a cause of physical activity, it is reasonable to hypothesize that physical activity is a moderating variable instead of a mediating variable. For instance, individuals who experience high amount stressful life events but are more physically active might experience less cognitive function decline, compared to those who have high amount stressful life events but are less active.

Psychosocial and behavioral factors may be important mechanisms that buffer against the deleterious effects of stressful life events. However, the possible ameliorating role of psychosocial and behavioral factors on the relationship between stressful life events and cognitive function has yet to be examined. Finding low-cost behaviors and internal resources that lower risk of cognitive decline is critical for the successful implementation of public health interventions that have the potential of affecting a high proportion of the US female population.

Purpose

While stressful life events have been operationalized as a stressor, no study has examined the pathways through which stressful life events may affect cognitive function. Specifically, no study has examined the effects of moderators and mediators in the context of the stress-cognitive function relationship using longitudinal data. The purpose of this study was to prospectively examine the pathways through which

stressful life events may affect cognitive function. The purpose of the study was addressed through answering the following research question and hypothesis:

R1: Is the relationship between stressful life events and cognitive function influenced by external and/or internal pathways?

H1: Both behavioral and psychological factors will contribute to lower cognitive function scores. External factors (e.g., physical activity, social support) will moderate and internal factors (e.g., hostility, optimism, negative expressiveness, ambivalence) will mediate the stress-cognition relationship. Specifically, those exposed to more stressful life events will have a less favorable psychological state, and in turn, the less favorable psychological state will be associated with lower cognitive function scores.

Methods

Theoretical Framework

The theoretical framework used to inform this investigation is based on the risk and protective factors of the stress process theory (Pearlin; Pearlin, Schieman, Fazio, & Meersman, 2005). This theory posits that accumulation of stressors, in particular, major life events and ongoing strains, can overburden an individual's ability to cope or adjust, increasing the risk of physical illness, injury, and disease. In general, the stress process theory mainly explains psychopathology of health outcomes in terms of exposure to stress and ameliorative factors, such as social support, personal attributes, and behavioral factors. Specifically, the mental and physical health consequences of stress exposure can be attenuated by external (e.g. physical activity) and internal (e.g. psychological) variables.

Three sources are identified (social, psychological, and physiological environments) as major contributing factors in the life stress process. In this paradigm, the three environments and their respective factors are identified as the exogenous concepts influencing health outcomes. The effects on the outcomes can be specified as direct effects, mediating effects, and moderating or buffering effects. Direct effects are self- explanatory. For example, social resources will have a direct impact on health, after controlling for alternate factors. A mediating effect of a factor on health occurs when its presence reduces or eliminates the direct impact of another exogenous factor on the health outcome. A typical example of the mediating effect would be social resources' ability to reduce the direct effect social stressors exert on the outcome. A

moderating or buffering effect is said to have taken place when the joint presence of two exogenous factors impacts the health outcome. A typical empirical model of this nature would be that a detrimental effect on a health outcome would only occur when one encounters stressors (e.g., life events), with the absence of social resources (e.g., the lack of social support). For the purposes of this study, physiological and psychological factors are hypothesized as mediating factors, while behavioral factors, specifically physical activity, are hypothesized as moderating factors (see Figure 2).

Several studies (Ensel and Lin 2000; Katerndahl and Parchman 2002; Taylor and Aspinwall 1996) and comprehensive reviews (Aneshensel 1992, 1999; Thoits, 1995) have documented the usefulness of this theory with respect to explaining physical and psychological health outcomes. However, the potential protective effects against the damage stress may cause are not entirely known. In particular, a comprehensive evaluation of how an individual's use of coping strategies, high levels of personal coping resources (e.g., cynicism, optimism, emotion regulation), and possession of socially supportive ties may attenuate the effects of stress against cognitive function are largely unknown.

Design

Data from the Women's Health Initiative Memory Study (WHIMS; *n* = 7,479), a subset of participants randomly selected from the WHI Hormone Therapy Trial (WHI HT), was used to address the research questions. The WHI is a large, multicenter investigation of postmenopausal women enrolled in one of the 3 randomized clinical trials (Hormone Therapy, Diet Modification or Calcium Vitamin D) or the Observational

Study. The WHI was initiated in 1992 and enrolled participants at one of 40 WHI clinical centers nationwide. Participants were followed annually up to 8.5 years (*M* = 5.2 yrs). The WHI HT was stopped early due to the unfavorable risk-to-benefit ratio and evidence of early harm (Writing Group for the Women's Health Initiative Investigators, 2002). The decision to stop the WHI HT also ended WHIMS.

To control for the possible effects of the intervention drug on the outcome, only participants randomized in the placebo groups were included for all analyses (*n* = 3775). Table 2 provides samples sizes for each group by data collection point. In addition, we only used data from 5 data collection points (baseline and follow-up years 1 through 4) due to the significant loss to follow-up after year 4.

Participants

WHIMS was a double-masked, placebo-controlled, clinical trial. Thirty-nine of the WHI clinical centers and 10 satellites participated in WHIMS. Participants in the WHIMS, an ancillary study to the WHI HT, were recruited between May 1996 and December 1999 from women in the WHI HT. A total of 7,480 women ages 65-79 were recruited from the WHI HT. Of the 7,480 women, 2,948 were in the estrogen only (E-alone) study for women without a uterus at the time they enrolled and 4,532 were in the estrogen plus progestin (E+P) study for women with a uterus at time of enrollment. Participants were followed annually up to 8 years (*M* = 4.5 yrs). To address all research questions, complete data on healthy women aged 65-79 years enrolled the WHI HT and the WHIMS were used. Of these combined cohorts, complete data are available for approximately *n* = 3775 healthy women who did not receive an active treatment.

Previous studies have shown a relationship between estrogen and cognition. Consequently, only participants in the control arms were used in order to eliminate all effects of hormone therapy.

Key exclusion criteria for participation in the WHI HT were the following: invasive cancer within the previous 10 years, major cardiovascular (myocardial infarction or stroke) disease events in the previous 6 months, medical conditions contraindicating for hormone therapy, systolic blood pressure > 200mmHg or diastolic blood pressure > 105mmHg. Key inclusion criteria for participation in the WHIMS were being 65 years or above and free of dementia. The Modified Mini-Mental Exam (3MSE) was used as a primary screening assessment of cognitive functioning (Teng & Chui, 1987) at baseline screening and then at annual follow-up visits. Those who scored below a set cutpoint, which were based on previous studies (Graham & Rockwood, 1997; Tombaugh et al., 1996), were scheduled for a more extensive neurocognitive assessment and neuropsychiatric examination.

Measures

All of the measures in this application have already been assessed on the WHI HT and WHIMS cohorts and are available through the public use data sets.

Dependent variable

Cognitive function

Global cognitive function was based on scores from the Mini-mental state exam (3MSE) collected at baseline and annually for up to 8 years. The 3MSE consists of 15 items that produce a range of possible scores from 0-100, with higher scores reflecting

better cognitive functioning. The 3MSE, a quantitative indicator of cognitive function widely used clinically and epidemiologically, has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia (Bravo & Herbert, 1997; McDowell et al., 1997). A score of < 88 on the 3MSE has been suggested as the optimal cutpoint to classify this sample of women (with education levels ≥ 9 years) with probable dementia or composite mild cognitive impairment/probable dementia, and a score of < 80 for those with < 9 years of education. Trained and certified technicians, who administered the 3MSE in the WHIMS, were masked to the treatment assignment of all participants.

Independent variable

Stressful life events

Participants completed a modified version of the stressful life events scale from the Alameda County Epidemiologic Study (Ruberman et al., 1984). This inventory was modified to ensure relevance to older women. The questionnaire was completed at baseline and again at all follow-up points for up to seven years. Participants responded yes or no as to whether any of 11 life changes had occurred over the past year: spouse died, spouse had serious illness, close friend died, had major problems with money, divorced or break up, close friend divorced, major conflict with children or grandchildren, lost job, physically abused, verbally abused, and pet died. Positive responses were summed, yielding a score ranging from 0 to 11 with a higher score indicating more life events. A previous study using participants from the WHIMS reported a M = 1.7, SD = 1.4. (Michael et al., 2009)

In addition, women were asked to appraise each life event that occurred based on the amount of upset that it caused based on a scale ranging from 1 (*did not upset me*) to 3 (*upset me very much*). This scale ranged from 0 to 33 with a higher score indicating a participant experienced a greater number of more stressful events (*M* = 3.3, *SD* = 3.2; (Michael et al., 2009).

In order to best capture the cumulative effects of repeated exposure to stressful life events, stressful life events variable was dichotomized into two groups: those who were exposed to three or more stressful life events at all data collection points and those who were exposed to less than three. In order to best capture the cumulative effects of repeated exposure to stressful life events, the stressful life events variable was dichotomized into two groups: those who were exposed to three or more stressful life events at all data collection points and those who were exposed to less than three. We chose a cutpoint of three stressful life events because we hoped to define those exposed to high levels of stress.

Potential Mediating Factors

Optimism. The Life Orientation Test–Revised is a 6-item scale designed to measure optimism. Each item is scored on a 5-point scale from “strongly disagree” to “strongly agree.” All items are then summed, yielding a total score that ranges from 6 to 30, with higher scores indicate greater optimism, and lower scores indicate greater pessimism. Sample questionnaire items are as follows: "In unclear times, I usually expect the best"; "If something can go wrong for me, it will." Generally, optimism scores are categorized into quartiles based on the sample distribution. An article published using

WHI data used the following cutoffs: Highest (≥26; "optimists"); mid-high (24–25); mid-low (22–23); and lowest (<22; "pessimists")(Tindle et al., 2009).

Cynical hostility. The cynicism subscale of the Cook-Medley Questionnaire was used to assess cynical hostility. This scale contains 13 true/false items, with false items assigned a value of 0, and true items = 1. Higher scores indicate greater cynical hostility. Sample items include, "I have often had to take orders from someone who did not know as much as I did," and "It is safer to trust nobody." Previously published articles using WHI data categorized cynical hostility scores into quartiles, using the following cutoffs: Most (≥6); mid-high (4–5); mid-low (2–3); and least (0–1) (Tindle et al., 2009). To have comparable results, this study used the same or similar cutpoints.

Emotional Expressiveness. Four items from King and Emmons' (King & Emmons, 1990) Emotional Expressiveness Questionnaire were used to assess emotional expressiveness. A six-week test-retest correlation on the original King and Emmons scale was 0.78 in a sample of 50 college students (King & Emmons, 1990). Currently, there is no support for the stability of these constructs among a population of midlife and older women.

Ambivalence and Emotional Expressiveness. Three items from King and Emmons' Ambivalence over Emotional Expressiveness Questionnaire were used to assess *ambivalence and emotional expressiveness.* Both scales were included in WHI baseline and follow-up questionnaires. Confirmatory psychometric analyses of the Emotional Expressiveness and Ambivalence over Emotional Expressiveness subscales were used to establish validity and reliability in the WHI cohort (Michael et al., 2005) and they found

that higher ambivalence was associated with lower quality of life, lower optimism and higher hostility.

Potential Moderating Factors

Physical activity

Physical activity behavior was measured using self-report procedures. Participants estimated the frequency and duration of walking and of several other types of activities that ranged in intensities (e.g., mild, moderate, and strenuous). To assess mild activities, a series of questions asked about walks outside the home for more than 10 minutes without stopping, average duration of each walk, and usual walking pace. Slow dancing, bowling, and golf were also considered mild activities. Moderate exercise was defined as activities that are "not exhausting", such as biking outdoors, using an exercise machine (e.g., stationary bicycle or a treadmill), calisthenics, easy swimming, and popular or folk dancing. Vigorous exercise was defined as activities during which "you work up a sweat and your heart beats fast," including aerobics, aerobic dancing, jogging, tennis, and swimming laps.

Weekly energy expenditure scores were converted to metabolic equivalents (MET score), using a standardized classification of the energy expenditure associated with physical activities. Data were collected every 3 years, over a 9 year period. The physical activity assessment questionnaire was found to have adequate reliability (weighted kappas among all women ranged from 0.67 to 0.71) (Langer et al., in press).

We decided operationalize physical activity according to federal physical activity guidelines. Federal guidelines recommend that older adults, aged 65 years and older,

should follow guidelines for adults: 150 minutes per week of moderate to vigorous intensity physical activity. To help elucidate at which physical activity or energy expenditure level an individual should achieve in order to garner the most benefit, two physical activity variables were created: total MET-hours per week and total time spent in moderate to vigorous physical activity per week. Both these variables were dichotomized according to federal guidelines.

Social support

Nine social support items were selected from the larger 15-item Medical Outcomes Study. The social support questionnaire indicated perceived availability of the components of functional support (Sherbourne & Stewart, 1991). Specifically, participants identified how often they have particular types of support available (e.g., someone to give good advice). All items were scored as none of the time, a little of the time, some of the time, most of the time, or all of the time. Previously published articles using WHI data assigned these items on a scale from 0 (none of the time) to 5 (all of the time). Scores were then averaged to create a single social support variable. To have comparable results, this study used the same calculation. No established, clinically meaningful cut-offs exist for the social support scale in the published literature (Hardy, Concato, & Gill, 2004). However, higher scores indicate more favorable social support.

Covariates

Sociodemographics

Age, r*ace/ethnicity*, *education and insurance status* were assessed via self-report questionnaires. Women self-identified as non-Hispanic white, black or African American, Hispanic or Latino, Asian/Pacific Islander, American Indian or Alaska Native, or other.

Comorbid conditions and physical factors

Diabetes. Participants self-reported if a physician had ever told them that they had "sugar diabetes" when they were not pregnant. Family history of diabetes was ascertained. *Body mass index (BMI).* BMI was calculated from height and body weight as follows: BMI (kg/m^2) = Body weight (kg) / Height $(m)^2$ and was used to classify subjects as normal weight, at risk for overweight or overweight using the cutpoints as recommended by the U.S. Centers for Disease Control and Prevention Centers for Disease Control and Prevention.

Cardiovascular disease. Family history of cardiovascular disease was ascertained.

Depression. Depressive symptoms were measured using the 6-item scale from the Center for Epidemiological Studies Depression scale (CES-D; (Radloff, 1977). For the CES-D, each item is scored as 0 (rarely or none of the time [<1 day]), 1 (some or a little of the time [1-2 days]), 2 (occasionally or a moderate amount of the time [3-4 days]), or 3 (most or all of the time [5-7 days]). Scores may range from 0 – 18, with a higher score indicating more symptoms of depression. A common cut point of the full 20-item CES-D

in screening for depression is a score of 16 or greater, out of a possible maximum score of 60 (Radloff, 1977). In a previously published article using WHI data, a cutpoint of 5 (out of a possible 18) was used to indicate depression (Wassertheil-Smoller et al., 2004). This cutpoint corresponds to the cutpoint point of 16 on the full scale.

Behavioral factors

*Smoking***.** Participants indicated number of cigarettes usually smoked each day.

Alcohol consumption. Alcohol consumption was determined from responses to a single two-part item. The first part categorized alcohol intake on a weekly/monthly level; the second part asked participants to indicate number of servings per week of beer, wine and/or liquor based on a medium serving size which is 12oz of beer, 6oz of wine and 1½ oz of liquor.

Antidepressant Use. To measure antidepressant use, participants were asked to bring all current medications to baseline interviews (WHI Clinical Coordinating Center).

Analysis

R5: Is the relationship between stressful life events and cognitive function influenced by external and/or internal pathways?

H5: Both behavioral and psychological factors will contribute to lower cognitive function scores. External factors (e.g., physical activity, social support) will moderate and internal factors (e.g., hostility, optimism, negative expressiveness, ambivalence) will mediate the stress-cognition relationship. Specifically, those exposed to more stressful life events will have a less favorable psychological state, and in turn, the less favorable psychological state will be associated with lower cognitive function scores.

Mediation analysis

Mediation was analyzed using analytic procedures recommended by Baron and Kenny (1986). A total of three regression equations were conducted for each mediating variable. The following example uses optimism as the mediator. For the first regression, the dependent variable (cognitive function) was regressed on the independent variable (stressful life events) to establish if there is an effect to mediate (see figure 3.1, path c). For the second regression, optimism was regressed on the independent variable, stressful life events, to establish if optimism is in the mediational pathway (see figure 3.1, path a). In the third regression, the dependent variable (cognitive function) was regressed on both stressful life events and optimism. This last

step is to provide evidence whether stressful life events are associated with cognitive function (see figure 3.1, path b), and to give an estimate of the relationship between stressful life events and cognitive function, controlling for optimism (see figure 3.1, path c'). All regressions adjusted for age, SES factors, smoking, alcoholic consumption, age at menopause, and history of cardiovascular disease.

To demonstrate that optimism functions as a mediator, the following conditions must be met: 1) the independent variable (stressful life events) must have an impact on the dependent variable (cognitive function); 2) in the second regression, the independent variable (stressful life events) must affect the mediator (optimism); and 3) for complete mediation, the mediator (optimism) must have an effect on the dependent variable (cognitive function) and the relationship between the independent variable (stressful life events) and the dependent variable (cognitive function) is no longer significant, in the third equation. For partial mediation, the mediator (optimism) must have an effect on the dependent variable (cognitive function) and the relationship between the independent variable (stressful life events) and the dependent variable (cognitive function) is significantly decreased.

Moderation analysis

Moderation is considered present if the interaction term is significant, regardless of the significance of the main effects. Following criteria established by Baron and Kenny (1986), three steps were performed to test if the association between the independent variable and the dependent variable varies as a function of the moderator. First, the moderating variable was changed from a continuous variable to a categorical

variable. For instance, assuming the interaction term of PA and stressful life events is significant, PA was then split into two categories, 'low' and 'high', using a median score cut-point based on average estimated energy expenditure. Second, regression analyses were used to examine the association between stressful life events and cognitive function decline among individuals with low and high PA scores.

Linear mixed models

To address R5, a linear mixed effects model, which combine fixed-effects regression methods (covariates) and a generalization of the variance components (site-level factors and time), was applied. Since all variables were collected at several time points, individual rates of change for each participant were obtained. To this effect, mixed effects linear models were fit with the proposed mediator or moderator as a function of time (for each data collection point), with a random participant-specific intercept and slope added to the model.

Covariates for the mixed models included race/ethnicity, age, year of data collection, SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease. Individual-level factors (e.g., SES, marital status, cohabitation status, smoking, caregiving responsibilities, alcohol consumption, social support, BMI, systolic and diastolic blood pressure, depression, social strain, diabetes, depression, and cardiovascular disease) were treated as fixed effects, and site-level factors and time were treated as random effects.

Linear mixed effects models were run using SAS PROC MIXED, which supports mixed effects models.

Results

Table 3.1 displays the variables of interest with corresponding assessment instrument. The average follow-up for participants enrolled in the estrogen-alone trial was 5.4 years and 4.06 years for those in the estrogen plus progestin trial. Due to significant loss to follow-up, we only included data up to and including data collection period year 4. Table 3.2 provides sample characteristics by data collection year. The average age at baseline for this combined sample was 70.1 (*SD* $\pm$ 3.85) years. The most often reported income was $20,000 to $34,999 (30%) and 53% of the sample were married or in a marriage-like relationship. Based on BMI, 29% of this sample had a BMI within the normal range (i.e., BMI = <25) while 35.9% were overweight (BMI = 25-29.9) and 34.4% were obese (BMI $\geq$ 30; data not shown). Approximately 66% of the sample had at least some college education. In addition, 53% of the women never smoked cigarettes and 63% did not provide informal care for an ill friend or spouse. All of the psychological variables remained steady over all data collection points, with no significant increases or decreases in scores.

Mixed effects analysis of all hypothesized mediators

Table 3.3 presents results of all potential mediating and moderating variables, after controlling for potential confounding variables. All potential mediating, moderating, and confounding variables were simultaneously entered into a mixed effects model. Of the psychological variables, hostility $(\beta = 0.05, p = 0.002)$, negative emotion expressiveness $(\beta = 0.23, p = 0.001)$, and optimism $(\beta = 0.04, p = 0.002)$ were significant.

Tables 3.4 – 3.7 display the results of the mediation analysis for each of the variables that were significant in Table 3.3. After controlling for possible confounders, three of the four variables met Baron and Kenny's requirements for partial mediation: hostility, negative emotion expressiveness, and optimism. Evidence of full mediation was met since the significant association between stressful life events was not evident when the psychological variable was entered in the third step. Specifically, lower levels of hostility (β = 0.07, p <0.0001) and negative emotion expressiveness (β = 0.19, p <0.004); and higher scores of optimism (β = 0.07, p <0.0001) were associated with higher cognitive function scores. In other words, there were positive relationships between hostility, negative emotion expressiveness, and optimism with cognitive function. To be more specific, for every 1 point increase in hostility, there is a 0.07 point decrease in cognition scores.

Mixed effects analysis of all hypothesized moderators

Table 3.8 presents results of the hypothesized physical activity moderating variables. Three separate mixed effects models were conducted in order to determine the presence of moderation. Specifically, an interaction term of stressful life events and the potential moderator (e.g., MET-hr/week, moderate-to-vigorous physical activity, and social support) were included in the model along with all confounding variables. The interaction terms for MET-hr/week (β = 0.15, p = 0.096), moderate-to-vigorous physical activity (β = -0.20, p = 0.130), and social support (β = 0.00, p = 0.473). Consequently, further analyses were not warranted.

Discussion

The primary purpose of this study was to prospectively examine the pathways through which stressful life events may affect cognitive function. Contrary to our hypothesis, behavioral factors such as physical activity did not moderate the stress-cognition relationship. Instead, our data seem to indicate that psychological variables, such as hostility, optimism, negative emotion expressiveness, and physical limitations significantly mediated the relationship between stressful life events and cognitive function. Previous research has suggested that optimism and hostility are associated with perceived stress, coping ability, and social support. Specifically, studies have reported that, compared to pessimists, optimists are more likely to cope with adversity in healthier ways (Scheier, Weintraub, & Carver, 1986) and to build stronger social relationships (Srivastava, McGonigal, Richards, Butler, & Gross, 2006).

Conversely, another study reported that hostility may reduce the stress-buffering effects of social support (Lepore, 1995). Similarly, the data suggest that individuals who had lower hostility scores, in spite of reporting at least three stressful life events at all data points, had higher cognitive function scores, compared to individuals with higher hostility scores. In other words, it appears that hostility may act as an underlying mechanism through which exposure to stressful life events affect cognition. Our results also indicate that optimism and negative emotional expressiveness provide another mechanism through which the negative effects of cumulative exposure to stressful life events on cognition may be ameliorated. While these relationships were modest in magnitude, it is nonetheless important to find

pathways that may offset or prevent any stress-related and/or age-related effects of cognitive function decline. It should be noted that the mean cognition scores for this sample slightly increased over time, indicating that our sample of post menopausal women were highly educated and high functioning. Hence, these results may not be generalizable to a lower functioning group of women with lower educational attainment.

Biologic plausibility of the mediators

There is preliminary evidence of a biologic pathway through which optimism may affect neural responses. In a neural imaging study, Sharot and colleagues (2007) suggest differential neural responses among optimists and pessimists (Sharot, Riccardi, Raio, & Phelps, 2007). Likewise, Shapiro and coworkers found different neural responses among hostile and nonhostile individuals. It is thought that these processes may contribute to more frequent or more severe experiences of negativity among pessimistic (Raikkonen, Matthews, Flory, Owens, & Gump, 1999) and hostile (Chen, Gilligan, Coups, & Contrada, 2005) individuals, which may negatively affect future cognitive function. Considering that the largest generation cohort, baby-boomers, are nearing retirement age, it becomes imperative to find factors that may help preserve cognition. To date, no previous study has examined potential protective or risk factors that may influence cognitive function.

It should be noted that, contrary to our hypothesis, physical activity did not affect the stress-cognition relationship. One possible explanation for the lack of significant moderation is that the cutpoints we used to indicate a person as being

physically active may not have been high enough. We choose to use these physical activity cutpoints in order to stay consistent with federal guidelines and because they are attainable for an older, female population. However, the level of physical activity that must be maintained over time in order to lower the risk of cognitive function decline may be higher than what is recommended by the federal government. Comparing highest to lowest level of physical activity may have produced different results, as indicated by previous data (Laurin et al., 2001; Weuve et al., 2004). Specifically, Weuve et al (2004) reported that women in the highest quintile of physical activity, compared to women in the lowest quintile, had 20% lower odds of cognitive impairment. Similarly, Laurin et al. (2001) found that women with the highest physical activity level had 42% and 37% lower odds of Alzheimer's Disease and dementia, respectively. It is also quite possible that there is a positive independent association between physical activity and cognition, whereby higher levels of physical activity are associated with higher cognitive function scores, but not an interactive association between stressful live events and physical activity on cognition. We were unable to perform an analysis using similar cutpoints as the previous studies since a relatively small proportion of our participants engaged in the top quintile of vigorous physical activity and the possibility of finding differences between lowest and highest levels of physical activity was quite low.

Another plausible explanation for the lack of moderation by physical activity on the stress-cognition relationship is due to the fact that this sample increased cognitive function scores at each subsequent data collection period. While this slight increase

was not statistically significant, it is in the opposite direction of previous literature that widely supports that cognitive function tend to decrease over time and that age is a significant risk factor for declines in cognition. Further, it is mainly thought that physical activity levels tend to decrease with age. However, the physical activity levels in this sample did not precipitously decrease as expected. In the end, the overall variance in cognitive function scores and physical activity was greatly limited and the chance of finding a statistically significant relationship in the expected direction was greatly reduced. Results from the Women's' Health Initiative Hormone Therapy trials also indicated that mean cognitive functions scores increased over the first four years, and that participants who received the active drug had a higher risk of developing dementia compared to those in the placebo (Espeland et al., 2004; Shumaker et al., 2003).

To our knowledge, this is the first study to provide a comprehensive overview of the relationship between stressful life events and cognition. Specifically, we were able to provide longitudinal evidence that stressful life events are compelling stressors that places individuals at increased risk for cognitive function decline and explain mediating variables through which stressful life events may affect cognition. While the magnitude of the protective effects that psychological factors appeared to present were quite small, it is still clinically relevant for the simple fact that preventing cognitive function decline may be just as important as improvement, in terms of health- and economic-benefit.

Strengths and limitations

There were several strengths of this study. We used a nationally representative sample of post-menopausal women who were enrolled in the largest randomized clinical trial of hormone replacement therapy. In order to eliminate effects of any intervention, only participants randomized into the placebo arms were used. Due to the relatively large sample size and multiple follow-up points, we were able to use mixed effects modeling, a statistical analysis that incorporated all data points (up to 4 years) for both the exposure and outcome variables. Unlike similar previous studies, we were also able to adjust for many confounders, such as depression, comorbidities, physical markers (e.g., BMI, blood pressure), and behavioral variables (e.g., smoking, alcohol drinking).

In spite of the study strengths, several limitations need to be acknowledged. Operationalizing stress as exposure to life events assumes that these events are perceived as negative and undesirable. Although this approach has a subjective component, it is less liable to reporting bias and variations in established discourse (Phillips et al., 2008). Some of the modified scales used for this study have not been previously validated among a cohort of older women. Further, we did not have any measures of a possible third pathway, biomarkers, through which stressful life events may affect cognition. All internal variables were assessed via self-report questionnaire and could be subject to recall bias.

The secondary nature of data analyses are limited to what was collected during the data collection points. Consequently, operationalization of all measures was based

on decisions made by WHI investigators. Assessment of all variables involved in addressing our specific research questions may not be ideal and not all possible confounding variables may be available. In addition, certain biases may have been introduced due to the prospective nature of the clinical trials. Specifically regarding recruitment and enrollment of minority women, data were not collected on the total number of women contacted or on women who chose not to make the initial contact. Therefore, it is impossible to discern differences between racial/ethnic groups with regard to willingness to participate in the WHI trials. While our sample appeared to be a highly functioning, well educated group, our results indicate that repeated exposure to certain life events may pose a risk in the maintenance of cognitive function skills.

Conclusion

Considering the number of individuals $\geq$ 65 years is set to dramatically increase as the baby boom generation ages and the prevalence of Alzheimer's disease is expected to double by 2025 and nearly triple by 2050 (Hebert et al., 2003) elucidating protective factors for cognitive function decline become imperative. Our results appear to provide modest evidence that psychological mechanisms are an important pathway through which stressful life events affect cognitive functioning over time among a representative sample of post-menopausal women. In the end, it appears psychological factors and physical activity may ultimately help preserve cognitive function.

Results Tables

Table 3.1. Study variables and instruments

Variable	Instrument
Independent Variable	
Life events stress	Modified from Alameda County Epidemiologic Study
Covariates	
Age, ethnicity, education	Questionnaire
Smoking	Questionnaire
Alcohol consumption	Questionnaire
Anti-depressant use	Sight examination of all medications
Cardiovascular disease history	Questionnaire
Diabetes	Self-report, Questionnaire
BMI	Measured, Questionnaire
Depression	Center for Epidemiologic Studies Depression Scale
Blood pressure	
Mediators or moderators	
Hostility	Cook-Medley Questionnaire
Optimism	Life Orientation Test–Revised
Negative emotion expressiveness	Medical Outcomes Study Social Support Survey
Perceived physical health	Short Form 36 Health Survey
Physical activity	Questionnaire
Social support	Medical Outcomes Study Social Support Survey
Dependent Variable	
Cognitive function	Modified Mini-Mental State Examination

Table 3.2 Variables of interest by data collection period.†

	Baseline	Year 1	Year 2	Year 3	Year 4
Mean Cognitive function (SD)	95.2 (4.3)	95.9 (4.0)	96.3 (4.1)	96.5 (3.9)	96.6 (4.3)
Mean hostility (SD)	3.7 (2.8)	3.7 (2.8)	3.6 (2.8)	3.6 (2.8)	3.5 (2.8)
Mean negative emotion (SD)	2.7 (0.6)	2.7 (0.6)	2.7 (0.6)	2.7 (0.6)	2.6 (0.6)
Mean optimism (SD)	23.1 (3.3)	23.0 (3.2)	23.0 (3.2)	23.0 (3.2)	23.2 (3.2)
Mean physical limitations (SD)	75.8 (22.2)	66.9 (25.8)	66.7 (25.8)	67.3 (25.3)	68.2 (25.2)
Social Support	35.6 (7.80)	35.8 (8.04)	35.8 (8.03)	35.9 (7.99)	35.9 (7.94)
MET-hrs per week	11.9 (14.32)	11.3 (13.33)	10.9 (13.21)	11.0 (13.39)	11.1 (13.39)
MVPA per week	89.1 (142.28)	83.9 (129.09)	79.8 (128.92)	81.2 (130.67)	82.2 (130.79)
Mean Age (SD)	70.1 (3.8)				

†All variables were coded such that a higher score indicates a more favorable psychological state (e.g., hostility: higher score indicates less hostility).
MVPA = moderate to vigorous physical activity.

Table 3.3 Results of longitudinal mixed effects analysis of all hypothesized mediators on cognitive function.[†]

Variable[a]	β	SE	*p*-value
Psychological			
Hostility	**0.05**	0.02	**0.002**
Negative emotional expressiveness	**0.23**	0.07	**0.001**
Optimism	**0.04**	0.01	**0.002**
Social functioning	0.00	0.00	0.225
Social strain	-0.02	0.02	0.077

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education.

[a]All variables were coded such that a higher score indicates a more favorable psychological state (e.g., hostility: higher score indicates less hostility).

Table 3.4. Results of longitudinal mixed effects analysis to determine if hostility mediates the relationship between stressful life events and cognition.[†]

Variable[a]	Unstandardized β	SE	*p*-value
Step 1: cognitive function was regressed on stressful life events			
3 stressful life events[b]	0.31	0.15	**0.035**
Step 2: hostility was regressed on stressful life events			
Hostility	0.09	0.01	**<0.0001**
Step 3: cognitive function was regressed simultaneously on hostility and stressful life events			
Hostility[c]	0.07	0.01	**<0.0001**
3 stressful life events	0.29	0.15	0.055

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education.

[a]A higher score indicates a more favorable psychological state (e.g., hostility: higher score indicates less hostility).

[b] Those reporting more than at least 3 stressful life events at all time periods were the reference.

[c]Evidence of partial mediation is present.

Table 3.5. Results of longitudinal mixed effects analysis to determine if negative emotional expressiveness mediates the relationship between stressful life events and cognition.[†]

Variable[a]	Unstandardized β	SE	*p*-value
Step 1: cognitive function was regressed on stressful life events			
3 stressful life events[b]	0.31	0.15	**0.035**
Step 2: negative emotional expressiveness was regressed on stressful life events			
Negative emotional expressiveness	0.24	0.06	**0.000**
Step 3: cognitive function was regressed simultaneously on negative emotional expressiveness *and stressful life events*			
Negative emotional expressiveness[c]	0.19	0.06	**0.004**
3 stressful life events	0.28	0.15	0.061

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education.

[a]A higher score indicates a more favorable psychological state (e.g., negative emotional expressiveness: higher score indicates less negative emotional expressiveness).

[b] Those reporting more than at least 3 stressful life events at all time periods were the reference.

[c]Evidence of partial mediation is present.

Table 3.6. Results of longitudinal mixed effects analysis to determine if optimism mediates the relationship between stressful life events and cognition.[†]

Variable[a]	Unstandardized β	SE	*p*-value
Step 1: cognitive function was regressed on stressful life events			
3 stressful life events[b]	0.31	0.15	**0.035**
Step 2: optimism was regressed on stressful life events			
Optimism	0.07	0.01	**<0.0001**
Step 3: cognitive function was regressed simultaneously on optimism and stressful life events			
Optimism[c]	0.07	0.01	**<0.0001**
3 stressful life events[d]	0.25	0.15	0.091

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education.

[a]A higher score indicates a more favorable psychological state (e.g., optimism: higher score indicates higher optimism).

[b] Those reporting more than at least 3 stressful life events at all time periods were the reference.

[c]Evidence of partial mediation is present.

Table 3.7. Results of longitudinal mixed effects analysis to determine if physical limitations mediates the relationship between stressful life events and cognition.[†]

Variable[a]	Unstandardized β	SE	*p*-value
Step 1: cognitive function was regressed on stressful life events			
3 stressful life events[b]	0.31	0.15	**0.035**
Step 2: physical limitations was regressed on stressful life events			
Physical limitations	-0.01	0.00	**0.017**
Step 3: cognitive function was regressed simultaneously on physical limitations *and stressful life events*			
Physical limitations	-0.01	0.00	**0.004**
3 stressful life events	0.29	0.15	**0.049**

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education.

[a]A higher score indicates a more favorable physical state (e.g., physical limitations: higher score indicates less physical limitations).

[b] Those reporting more than at least 3 stressful life events at all time periods were the reference.

Table 3.8. Results of prospective mixed effects analysis to determine if physical activity or social support moderates the relationship between stressful life events and cognition.[†]

Variable	Unstandardized β	SE	*p*-value
Multivariate mixed effects			
3+ stressful life events[a] X MVPA[b]	-0.15	0.09	0.096
3+ stressful life events X MET-hrs[c]	-0.20	0.08	0.130
3+ stressful life events X Social Support	0.00	0.02	0.473

[†]All models controlled for the effects of age, year, ethnicity/race, income, marital status, smoking, alcohol consumption per week, cohabitation status, location, placebo arm, age at menopause, and education. Those meeting recommendations were reference category for all models.

MVPA = Moderate to vigorous physical activity.

[a]Those reporting more than at least 3 stressful life events at all time periods were the reference.

[b]Scores were categorized based on meeting 150 minutes of moderate to vigorous physical activity per week

[c]Scores were categorized based on meeting $\geq$ 500 MET-minutes per week or $\geq$ 8.33 MET-hours per week.

Figure 3.1. Effects without mediation

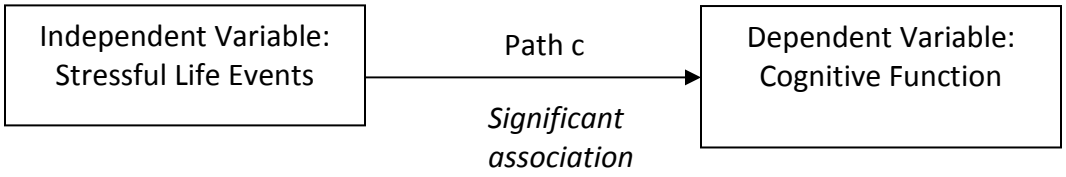
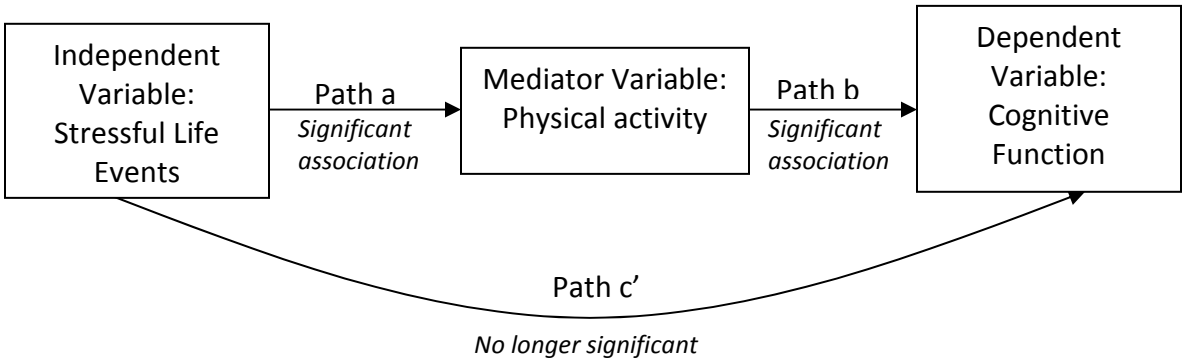


Figure 3.1: Effects with mediation



CHAPTER 5: Dissertation Discussion

The primary aim of this dissertation was to investigate whether stressful life events is a risk factor for lower cognitive functions scores over time. To this end, we sought to determine if individual life events or a cumulative exposure of stressful life events were associated with cognition. Given a negative relationship between stressful life events and cognition, a secondary aim was to investigate which factors may ameliorate the negative effect of stressful life events on cognitive function scores. Specifically, we examined the possible moderating and mediating roles of external and internal factors on the stress-cognition relationship.

Dissertation conclusions

It appears there are four main findings from this study. First, our data provide support that exposure to a single item on the stressful life events checklist, reporting an ill spouse/partner, was associated with lower cognitive function scores; whereas the sum score of the stressful life events, weighted or unweighted, was not related to cognition. Our results are similar to what Rosnick and colleagues reported such that single items and not the sum score were associated with worse memory performance. While the effect sizes were relatively small, it should be noted that the odds of scoring below 88 were modest. Specifically, the odds of falling below a cutpoint that indicates risk of cognitive function decline were 58% higher for women who reported having at least three stressful life events at all time points compared to women who did not have at least three stressful life events at all time points. The odds were even greater for women exposed to an ill spouse. For those who reported having an ill spouse, the odds

of scoring below the cutpoint was more than 2 times greater compared to women who did not report an ill spouse. Only three prior studies have assessed the association between stressful life events and cognition. However, this is the first study to overcome methodological issues which plagued previous studies. Specifically, we had a large sample size, took full advantage of longitudinal data, and controlled for many possible confounding variables. Based on the strengths, we are confident our findings add to existing literature indicating that certain stressful life events may be associated with lower cognition.

Second, our results appear to indicate that meeting physical activity recommendations was marginally associated with higher cognitive function scores. Women who did not achieve at least 500 MET-minutes per week appeared to have lower cognitive function scores compared to those who met guidelines, after controlling for several confounding factors. These results are consistent with previous findings (Laurin et al., 2001; Weuve et al., 2004) that suggest those who do not engage in any physical activity are at higher risk for cognitive function decline compared to those who engage in some physical activity. It should be noted that these results were detected in spite of our sample not showing in significant decline in cognitive function, as evidenced by the 3MSE scores, and physical activity levels did not precipitously decline through the follow-up years. Further, our sample was a highly educated, highly functioning group of women who may not accurately represent all postmenopausal women in the United States. Based on our results, there is modest evidence that physical activity may protect against lower cognitive function scores.

Third, external factors, such as physical activity and social support, did not appear to moderate the negative relationship between stressful life events and cognition. This could in part be due to methodological issues discussed earlier, the level of physical activity that must be maintained over time in order to lower the risk of cognitive function decline may be higher than what is recommended by the federal government, or a combination of both. It should be noted that the women in our sample were well below physical activity recommendations.

Last, our results appear to provide modest evidence that internal or psychological variables, such as hostility, optimism, and negative emotion expressiveness significantly mediated the relationship between stressful life events and cognitive function. Previous research has suggested that optimism and hostility are associated with perceived stress, and coping ability. Specifically, studies have reported that, compared to pessimists, optimists are more likely to cope with adversity in healthier ways (Scheier et al., 1986) and to build stronger social relationships (Srivastava et al., 2006). The magnitudes of the effect of the psychological variables are relatively small; however, it should be assessed within the context of the cognition scores. Specifically, these differences were found in spite of cognitive function scores increasing over time. To our knowledge, this appears to be the first study to provide a comprehensive overview of the pathways through which stressful life events may impact cognition.

Overall limitations

While this study was able to take advantage of longitudinal, multiple data points, using a large sample size, these results must be interpreted cautiously. One of the biggest limitations is not being able to control for the effects of having the APOe4 allele. We also had a relatively short follow-up time of only four years. In order to detect large declines in cognition, lengthy follow-up times are recommended. Unfortunately, for a randomized clinical trial of this scope and size, this was not feasible.

It must be acknowledged that the statistically significant differences we reported were relatively small. In addition to the characteristics of this highly educated sample, there are several other possible contributing factors that may help explain the small effect sizes and lack of moderation. First, the cognition scores slightly increased over four years, which is in the opposite direction as expected. Again, this might be a reflection of the high educational attainment of this sample and the fairly short follow-up period. Second, the average physical activity levels did not precipitously drop off as expected and the women achieved only 60% of the recommended levels of weekly physical activity. Third, a very small proportion of women in this sample scored below their respective cutpoints (i.e., < 88 for those with $\geq$ 9 years of education, <80 for those with < 9 years of education), greatly reducing the power to detect differences. Based on these factors, it is not surprising that we detected small effect sizes.

Implications for practical applications

Considering that the largest generation cohort, baby-boomers, are nearing the age category at which dementia and cognitive function decline are detected, it becomes

imperative to find factors that may help preserve cognition. Based on the results of our study, it appears that people exposed to an ill spouse/partner or those repeatedly exposed several life events may be at greater risk cognitive function decline. In addition, those who react less favorably to stressful life events may be higher risk as well. Specifically, we found that exposure to higher levels of stress (i.e., three or more stressful life events) was associated with lower cognition scores. While this association was statistically significant, the effect sizes were less than a point difference on the 3MSE.

Our results also seem to indicate that several variables may help protect against lower cognition scores. Specifically, physical activity was appeared to have a slight protective effect, such that exposure to higher levels of physical activity was associated with higher cognition scores. Again, differences between high and low levels of physical activity were less than one point on the 3MSE. Further, our results appear to indicate that psychological variables were in the direct pathway through which stress may affect cognition. Our mediation analyses revealed that: 1) there was a negative relationship between stressful life events and cognition; and 2) more favorable states of hostility, optimism, and negative emotional expressiveness were associated with slightly higher cognition scores.

Unfortunately, physical activity did not moderate the negative relationship between stressful life events and cognition, meaning the relationship between stressful life events and cognition did not vary by the level of physical activity. However, physical

activity was directly associated with cognition. For instance, higher levels of physical activity was associated with higher score in cognition.

Within the overall theoretical model of direct and indirect pathways through which stressful life events may affect cognition, our data appear to suggest that: 1) stressful life events is directly and negatively associated with cognition; 2) hostility, optimism, and negative emotional expressiveness were indirectly associated with the stress-cognition relationship. Specifically, exposure to more stressful life events was negatively associated with psychological states; in turn, less favorable psychological states were associated with lower cognition scores; and 3) hypothesized moderators such as physical activity and social support were not indirectly associated with the stress-cognition relationship.

The small effect sizes should be considered within the context of how cognition was assessed and the limitations of the mini-mental state exam. Specifically, the mini-mental state exam is argued to be a relatively easy test of cognition. Given the high educational level of this sample and the ease of achieving a fairly high score, small changes in cognition may not necessarily be clinically unimportant and may be economically beneficial. A previous study reported that preventing only a 2-point decrease in the mini-mental exam is associated with an economic savings of ~ $3,700 (Jonsson et al. 2002). It should be noted that range for this scale was from 0 – 33. The modified mini-mental state exam used for this study had a much higher range of scores (0-100). With this higher range of scores in mind, preventing only a 1-point decrease may be associated with similar economic savings. Further, our results appear to provide

a detailed overview of the relationship between stress and cognition among a highly educated, highly functioning group of older women. Hence, prevention or intervention strategies may be tailored to those who are at greater risk based on these findings.

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