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The Potential Mediating Effects of Social Support Network Size and Physical Activity on Cognitive Function and Mortality Risk

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THE POTENTIAL MEDIATING EFFECTS OF SOCIAL SUPPORT NETWORK SIZE AND PHYSICAL ACTIVITY ON COGNITIVE FUNCTION AND MORTALITY RISK

By

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List of Abbreviations

ACE-R	Addenbrooke's Cognitive Examination Revised
ADAS-Cog	Alzheimer Disease Assessment Scale
AD	Alzheimer's Disease
CHD	Coronary heart disease
CI	Confidence interval
CRP	C-Reactive Protein
CVD	Cardiovascular disease
CV	Cardiovascular
DBP	Diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSST	Digit Symbol Substitution Test
EKG	Electrocardiogram
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazards ratio
LTPA	Leisure time physical activity
MCI	Mild cognitive impairment

MET	Metabolic equivalent of task
MMSE	Mini Mental State Examination
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
PA	Physical activity
SAS	Statistical analysis software
SBP	Systolic blood pressure
SICF	Short Index of Cognitive Function
TPAV	Total physical activity volume
WAIS	Weschler Adult Intelligence Scale

Abstract

BACKGROUND: Low cognitive function has been shown to be an independent predictor of all-cause and cardiovascular disease (CVD)-related mortality. Social support network size and total physical activity volume (TPAV) are two modifiable factors which have been shown to be independently associated with cognitive function and mortality risk. Therefore, the purpose of this study was to examine the potential mediating effects of social support network size and TPAV on cognitive function and all-cause and CVD-related mortality risk in a large, nationally representative sample of U.S. adults.

METHODS: Study sample (N =2,550) included older adult (≥ 60 years of age) participants in the 1999-2002 National Health and Nutrition Examination Survey. Quartiles of cognitive function were created using Digit Symbol Substitution Test scores. Social support network size was determined using the number of reported close friends. TPAV was determined from self-reported domestic, transportation, and leisure time physical activity.

RESULTS: Regression analysis revealed an approximate three-fold increase in all-cause and CVD-related mortality risk in participants in the lowest quartile of cognitive function, compared to the highest quartile of cognitive function. These relationships are independent of social support network size and TPAV. Linear and non-linear inverse dose-response relationships were also revealed between cognitive function and increased all-cause and CVD-related mortality risk, respectively (P for trend for both $P < 0.0001$).

CONCLUSION: In a large, nationally representative sample of U.S. older adults, low cognitive function was associated with increased all-cause and CVD-related mortality risk. However, both relationships were independent of social support network size and TPAV.

Chapter One: Introduction

Cognitive function has been defined as the performance of mental processes including perception, learning, memory, understanding, awareness, reasoning, judgement, intuition, and language (1). Different domains of cognitive function have been identified and include language, learning and memory, social cognition, complex attention, executive function, and perceptual-motor function (2). Different domains of cognitive function are also differentially influenced by aging. Executive function, new learning, working memory, prospective memory, visuospatial judgement, and the ability to perceive spatial orientation decline with age (3). However, language, immediate memory, and procedural memories remain relatively stable with aging.

Throughout the aging process, cognitive function has important implications for longevity. In middle aged and older populations, low cognitive function has been shown to be associated with all-cause and cardiovascular disease (CVD)-related mortality (4-6). Several mechanisms have been proposed to account for the association between low cognitive function and mortality risk, including health literacy, frailty, and the beginning pathophysiology of dementia (6).

When examining modifiable factors related to the relationship between cognitive function and mortality which may be targeted, social support and physical activity have been shown to be independently related to cognitive function and mortality. In high-functioning older adults, greater baseline emotional support has been predictive of better cognitive function following 7.5 years of follow-up (7). Additionally, lower levels of social support (or an absence of social support) have been shown to be linked to an increased mortality risk. In a 2013 meta-analysis analyzing the associations between social support and all-cause mortality risk, individuals with lower levels of social support exhibited a significant increase in all-cause mortality risk (8). When examining the relationship between physical activity and cognitive function, physical

activity has been posited to attenuate cognitive decline through increasing high-density lipoprotein cholesterol (HDL-C), lowering systolic blood pressure, and generally improving CVD-related risk (9). In older adults ≥ 65 years of age, physical activity has been shown to be inversely associated with all-cause mortality risk (10).

This chapter includes relevant background information pertaining to cognitive function, social support, and physical activity, which is followed by a focused literature review regarding the relationship between these variables. This chapter concludes with the purpose and significance of the research, a project description, and limitations inherent to the study design.

Background

Cognitive Function

Cognitive deterioration is a normal aspect of the aging process (3, 11). In a 2014 cross-sectional study, Hoogendam et al. (11) reported that the effect of age on cognitive function was already apparent in adults 45 years and older. These investigators found that a general cognitive factor (i.e., analysis incorporating elements of the Stroop Test, Letter-Digit Substitution Task, verbal fluency test, 15-word verbal learning test, design organization test, and the Purdue pegboard test) showed decline starting at age 45 and a quadratic effect of age was found for both the general cognitive factor and the Mini-Mental State Examination. Therefore, cognitive decline does not occur suddenly in older adulthood, but can begin in middle age with declines in general cognition, suggesting the importance of identifying factors which may attenuate age-related cognitive decline.

A rapidly aging population can indicate an increasing prevalence of age-related cognitive decline and neurocognitive disease. An estimated 14.5% (46.3 million) of the U.S. population were aged 65 or older in 2014 and this is projected to approximately double and reach 23.5% (98 million) by 2060 (12). With an increase in the proportion of older adults living in the United States (U.S), the prevalence of neurocognitive disorders can be expected to increase. In 2020, the prevalence of mild cognitive impairment (MCI), an intermediate stage between normal cognitive function and dementia, was 22.7%, and the prevalence of clinical Alzheimer's Disease (AD) was 11.3% in the United States (13). With an increasing prevalence of MCI, dementia risk concurrently increases because individuals with MCI have a high rate of progression to dementia (14). Moreover, it is not only important to identify factors which may attenuate age-related

cognitive decline, but it is important to identify factors which limit the progression from MCI to dementia.

During the aging process, functional, and structural changes occur in the brain which influence cognition and may contribute to the process of cognitive decline or the pathophysiology of neurocognitive disease. First, aging differentially affects the various domains of cognitive function. While speech, language, immediate memory, and procedural memory remain relatively stable with age, more complex cognitive tasks such as selective attention, divided attention, recent memory, prospective memory, executive function, processing speed, and visual perceptual judgment decline with age (3, 11, 15). Changes in brain structure also occur during the aging process which augment the process of cognitive decline. In the brain, gray matter includes the cerebral and cerebellar cortex which consists predominantly of cell bodies and dendrites and white matter includes the regions of the brain with myelinated axons connecting gray matter structures (3). While both gray matter and white matter are affected by aging, gray matter loss is most prominent in the prefrontal cortex, while the greatest white matter loss occurs in the frontal lobe and corpus callosum. Because the most important function of the prefrontal cortex is executive function, grey matter loss in the prefrontal cortex may account for the decline in executive function associated with age (16). Age-related changes are also found in the temporal lobes, where decreases in the volume of the hippocampus have been observed, subsequently influencing memory throughout the aging process (15). The importance of synaptic density has also been highlighted in dementia research, indicating that symptomatic dementia occurs when there is at least a 40% loss of neocortical synapses (3).

Moreover, cognitive decline is an inherent component of the aging process. However, cognitive decline and low cognitive function have deleterious effects on health outcomes.

Cognitive function has been shown to be associated with both all-cause and cause-specific mortality (i.e., death from cancer, CVD, and respiratory illness) (4-6, 17-18). In addition, cognitive function has been associated with a variety of other health outcomes including quality of life (19) and non-fatal CVD events including angina pectoris, myocardial infarction, and stroke (20). Because age-related changes in cognitive function have been established, assessment of cognitive function throughout the aging process remains important due to its implications for prognosis. Additionally, because mortality risk, quality of life, and CVD risk may be linked to modifiable lifestyle factors such as social support and physical activity, it remains important to examine how these factors influence the association between cognitive function and health outcomes.

Social Support

Social support has been defined as assistance which is accessible to an individual through social ties to other individuals, groups, and/or the larger community (21). The three most common types of social support include emotional, instrumental, and informational support (22). Emotional support is characterized by the availability of esteem, trust, concern, and listening. Instrumental support consists of the provision of tangible support, such as in aid or labor. Lastly, informational support is the availability of advice or information.

The presence, or absence, of social support has important implications for health outcomes. Social isolation and low levels of social support have been shown to be associated with mortality (7, 23), depression (24), and coronary heart disease (CHD) (25). The effects of social support on life expectancy have been reported to be as strong as the effects of obesity, cigarette smoking, hypertension, and physical activity level (26). Social support has been posited to improve health outcomes by targeting an individual's psychological state, behavior, and

response to stress (22). This phenomenon occurs as social support reduces CV reactivity to acute stress (27). Consequently, a lack of social support is associated with increased sympathetic nervous system activation and can result in increased levels of urinary norepinephrine, increased levels of plasma adrenaline, and elevations in both systolic and diastolic blood pressure (27). Additionally, social support may improve both mental and physical health by influencing behavior and reducing the rate at which individuals engage in risky behaviors, prevent negative appraisals, and increase treatment adherence (26).

Social support has also been shown to be associated with cognitive function. In a 2021 systematic review, a positive association was observed between social support and cognition (28). Social support included emotional support, satisfaction with support, positive or negative interactions, instrumental support, informational support, someone to share personal feelings and experiences with, and help with decision making. Among the 22 studies examined, global cognition (i.e., assessed with measures of global or composite cognitive function) was most frequently associated with social support and emotional support was associated with improvements on four out of five global cognition measures. In older adults, lower levels of social support were associated with a greater probability of cognitive deterioration. Therefore, social support may be an important target in order to maintain cognitive function in older adulthood. These investigators also examined the association between social networks and cognitive function. Social networks were defined as living arrangements, marital status, number of social ties, or frequency of contact with friends and family. Social network size and higher frequency of contact was also associated with global cognition.

The association between social support and cognitive function may be partially explained by the interactional brain hypothesis. The interactional brain hypothesis suggests that interactions

with others are a constitutive component of brain development and cognitive processes, regardless of whether the social interaction is virtual, implied, real, imagined, momentary, or continuing (29). Therefore, this theory suggests that social interactions with others in old age may function to maintain cognitive processes during aging. However, it should also be noted that changes in the characteristics of social relationships could occur because of cognitive decline, as opposed to being the cause of cognitive decline. In old age, cognitive decline may result in a generalized inability to function socially and lead to social withdrawal due to a failing memory or word-finding difficulties which attenuate self-efficacy (28).

Physical Activity

Physical activity has been defined as any bodily movement which is produced by skeletal muscles and results in energy expenditure (30). Four domains of physical activity have been established which include leisure time physical activity, occupational physical activity, transportation physical activity, and domestic physical activity. Leisure time physical activity consists of physical activity an individual engages in during their free time which is often based on interests and needs (31). By contrast, occupational physical activity is associated with an individual's physical job requirements. Next, transportation or commuting physical activity consists of physical activity performed when moving from place to place. Lastly, domestic physical activity consists of physical activity performed while working at home such as housework, gardening, general maintenance, or caring for one's family (32).

Similar to cognitive function and social support, physical activity has been shown to be positively associated with several health outcomes including CVD, quality of life, and depression. A 2012 meta-analysis of prospective cohort studies reported significant reductions in CVD risk (i.e., risk of incident CHD and stroke) in men and women engaging in a high level of

leisure time physical activity and a moderate level of occupational physical activity (33). When assessing the association between physical activity and quality of life, a 2012 systematic review reported that higher levels of physical activity were associated with better perceptions of quality of life in older adults, apparently healthy adults, and adults with various health conditions including CVD, overweight/obesity, hypertension, diabetes, and cancer (34). Lastly, increased physical activity volume has been shown to be inversely associated with depression levels and symptoms in individuals of all ages (35).

Physical activity is also important for maintaining longevity. A 2008 meta-analysis conducted by Nocon et al. (36) reported that physical activity is associated with a marked reduction in CVD-related mortality and all-cause mortality. The researchers found that changes in physical activity volume are important for reducing mortality risk in those who may be insufficiently active or sedentary, in addition to baseline physical activity level. In a 2019 population-based cohort study, long term increases in physical activity volume were associated with significant reductions in all-cause, CVD-related, and cancer-related mortality (37). These investigators also reported that meeting and maintaining the World Health Organization minimum physical activity guidelines of 150 minutes/week of moderate-intensity physical activity could potentially prevent 46% of deaths associated with physical inactivity.

Physical activity has also been shown to enhance existing cognitive function and prevent or delay the progression of cognitive disease (38, 39). In older adults, both acute and long-term moderate to vigorous intensity physical activity have been shown to improve brain structure, brain function, and cognition (39). This was supported by a 2019 prospective cohort study examining the associations between physical activity and trajectories of cognitive performance over a maximum 27-year follow up in community dwelling older adults (40). These investigators

reported that current physical activity was associated with better cognitive function on all cognitive tests (i.e., the Mini-Mental State Exam, Trails Making Test Part B, category fluency tests, and the Buschke-Fuld Selective Reminding Test) with advancing age. The investigators also noted that the highest global cognitive function throughout aging was maintained in individuals who were physically active (i.e., engaging in any level of physical activity at least three times per week) at age 30 and older, suggesting that physical activity in early life may promote brain changes and establish a "cognitive reserve" which may protect against cognitive deficits in older adulthood.

Not only is physical activity important for maintaining and improving cognitive function during normal aging, but physical activity can influence an individual's progression and risk of neurocognitive disease. There is strong evidence that greater amounts of physical activity reduce the risk for cognitive impairment in individuals at risk for dementia and cognitive impairment (39). In adults with dementia, there is moderate evidence suggesting that physical activity may improve cognitive function. Therefore, not only can increased physical activity volume attenuate the effects of age-related cognitive decline, but it can also be utilized to reduce the risk of neurocognitive disease and improve prognosis following diagnosis.

Focused Literature Review

Existing literature has demonstrated an increased mortality risk for those with low cognitive function, while establishing inverse associations between increased cognitive function, social support, physical activity volume, and mortality risk. These associations have been established independent of one another, and there are few investigations determining whether social support and physical activity mediate the association between cognitive function and

mortality risk. Furthermore, data examining these associations in large, nationally representative samples of the U.S. population are sparse.

Purpose and Significance

The purpose of this study is to examine the potential mediating effects of social support and physical activity on the association between cognitive function and all-cause and CVD-related mortality risk in a nationally representative sample of U.S. older adults ≥ 60 years of age. The primary aim of this study was to examine the following:

1. Do social support and total physical activity volume (TPAV) mediate the association between cognitive function and mortality risk?

To the extent of our knowledge, this is the first study to examine whether social support and TPAV mediate the association between cognitive function and all-cause and CVD-related mortality risk in a nationally representative sample of U.S. older adults ≥ 60 years of age who participated in the 1999-2002 National Health and Nutrition Examination Survey (NHANES). It was hypothesized that social support network size and TPAV mediate the relationship between cognitive function and mortality risk, due to the independent associations between the variables.

Project Description

The NHANES is a continuous program conducted by the National Center for Health Statistics which collects data about the health, nutritional status, and health behaviors of the non-institutionalized civilian population of the U.S. by combining personal interviews with standardized physical examinations and laboratory tests (41). The final sample in this study consisted of 2,550 men and women ≥ 60 years of age in the 1999-2002 NHANES. Cox proportional hazards regression analysis was conducted to determine the cumulative risk of all-

cause and CVD-related mortality according to cognitive function level. Limitations inherent to the study design include:

1. The inability to track potential changes in cognitive function between initial measurement and death.
2. Causality cannot be established due to the cross-sectional design of the study.

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Chapter Two: Review of Literature

Cognitive function has been established as an independent risk factor for all-cause and CVD-related mortality risk in middle aged and older adults (1-5). In a 2003 study examining the association between cognitive function and all-cause mortality in middle aged adults (48-67 years of age), higher cognitive function was associated with significant reductions in all-cause mortality risk (1). These investigators concluded that cognitive function assessed in middle age appears to have prognostic value for life expectancy similar to that reported in older adults. In a subsequent 2020 study examining adults ages 45-72 years of age, investigators found that both a composite score of cognitive function and individual measures of cognitive function (i.e., measures of immediate verbal recall, delayed verbal recall, semantic verbal fluency, and cognitive speed and attention) were associated with all-cause and CVD-related mortality during 10-years of follow-up (2). Baseline cognitive function has also been shown to be predictive of all-cause mortality in older community dwelling adults (3) and the association between cognitive function and all-cause mortality risk has been shown to be independent of CVD biomarkers (i.e., mean arterial pressure, high-sensitivity CRP, high-density lipoprotein cholesterol (HDL-C), total cholesterol, glycosylated hemoglobin (HbA1c), and body mass index (4).

Because of the established role of cognitive function as an independent risk factor for all-cause and CVD-related mortality, it is important to identify factors that may mediate this association to attenuate mortality risk. Social support and physical activity are two lifestyle factors which have been shown to be independently associated with both cognitive function and mortality. Therefore, social support and physical activity may be potential factors which mediate the association between cognitive function and mortality.

Social support has been shown to independently predict cognitive functioning independent of socio-economic status, health behaviors, and physical health (6). Better cognitive

function has been found in individuals with larger social networks and social participation (6), while poor social relationships have been associated with greater levels of cognitive decline (7). In older adults, different aspects of social relationships have been shown to influence cognitive function. Social activity (i.e., attending social interactions, field trips, travel, outings, visiting and receiving visitors, participation in voluntary activities, religious activities, membership in community groups, or social groups) has been shown to be positively associated with global cognition, executive function, working memory, visuospatial abilities, and processing speed in healthy, older adults (8). Global cognition is also positively associated with social networks (i.e., living arrangements, marital status, number of social ties or frequency of contact with friends and family) and social support (i.e., emotional support, satisfaction with support, positive or negative interactions, instrumental support, or informational support) in older adults.

An association between social support and mortality has also been established. A 2013 meta-analysis analyzing the association between social support and all-cause mortality found that individuals with lower levels of social support exhibited an average 11% increase in all-cause mortality risk and the importance of having social support increased with age (9). Moreover, social support has been posited to be a function of an individual's social network, highlighting the importance of examining the role of social support network size when relating social support to mortality. This was supported by a 2017 longitudinal study which found a 33% reduction in all-cause mortality risk in older adults ($\geq$ 60 years of age) with a social support network size of greater than or equal to 9 members (10).

Physical activity has also been shown to be related to cognitive function. Physical activity induces important structural and functional changes in the brain which improve brain plasticity and subsequently influence cognitive function and overall wellbeing (11). Physical activity is

also a protective factor against neurodegeneration (11). In older adults at risk for Alzheimer's Disease, significant improvements in cognitive function were observed following a six-week physical activity intervention when compared to participants who completed usual care (12). Improvements in cognitive function following a physical activity intervention have also been observed in healthy adults. In a 2010 meta-analysis of healthy adults ≥ 18 years of age, aerobic exercise was associated with a modest improvement in neurocognitive function (i.e., improvements in attention, processing speed, executive function, and memory) (13).

Terminology

Cognitive function refers to multidimensional mental abilities which include learning, thinking, reasoning, remembering, problem solving, decision making, and attention (14). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) identifies six domains of cognitive function including language, learning and memory, social cognition, complex attention, executive function, and perceptual-motor function (15). Within each domain of cognitive function, the DSM-5 has also established subdomains of cognitive function. Figure 1 illustrates the six domains and subdomains of cognitive function.

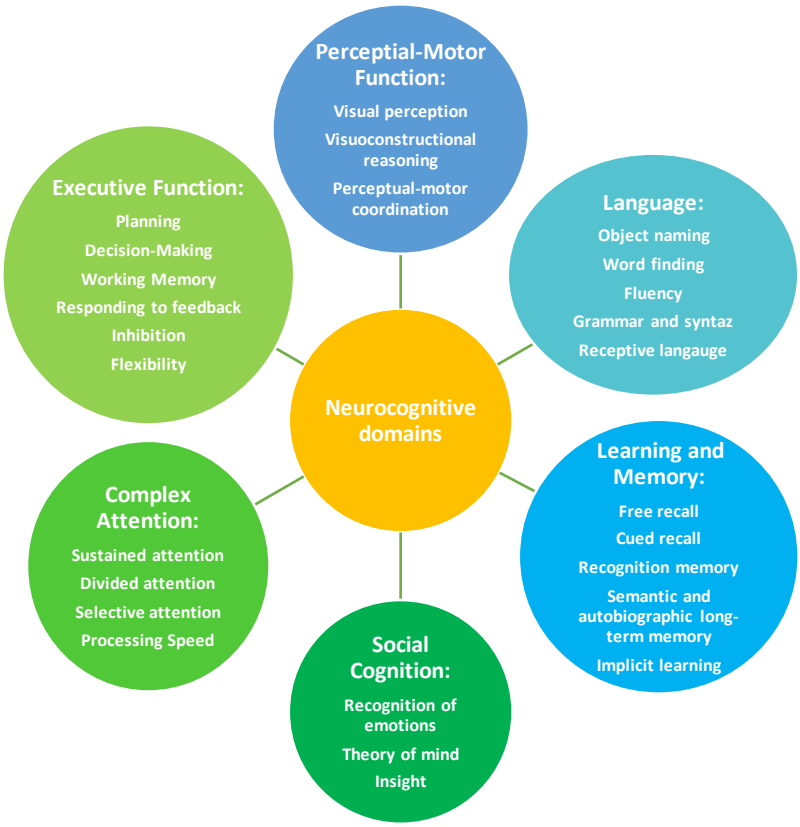

Figure 1. Neurocognitive Domains according to the DSM-5.

Note. Adapted from, "Classifying Neurocognitive Disorders: The DSM-5 Approach" by Sachdev et al. *Nature Reviews Neurology*. 2014;10(11), 634-642.

Social support has been defined as support which is accessible to an individual through social ties to other individuals, groups, or the larger community (16). Social support network size has been defined as a personal network which consists of people (e.g., a spouse, children, relatives, neighbors, friends, fellow members of organizations, and acquaintances) the individual has direct, personal relationships with (17). Within NHANES, social support network size has been characterized using the self-reported number of close friends (18-20).

Physical activity has been defined as any bodily movement produced by skeletal muscles which results in energy expenditure (21). There are four domains of physical activity which include leisure-time physical activity, occupational physical activity, transportation physical activity, and domestic physical activity. Leisure-time physical activity describes the activities an individual participates in during their free time which are based on personal interests (22). By contrast, occupational physical activity describes physical activity associated with the performance of a job. Transportation physical activity consists of physical activity performed with the purpose of going somewhere (e.g., walking, bicycling, climbing/descending stairs to public transportation) (23). Lastly, domestic physical activity consists of housework, yard work, childcare, chores, or self-care.

Cognitive Function

Cognitive function is an important predictor of health outcomes and different components of cognitive function are predictive of the development of neurodegenerative disease. In 2006, Bennett et al. conducted a prospective cohort study to examine how cognitive function is related to Alzheimer's Disease pathology (24). These investigators reported that the average global cognitive score was approximately 0.6 units lower for each unit of global disease pathology (i.e., based on a composite score of the number of neuritic plaques, diffuse plaques, neurofibrillary tangles, and amyloid-β deposits). These investigators concluded that cognitive function is inversely related to Alzheimer's Disease pathology. A subsequent 2009 study analyzed the associations between premorbid cognitive function, current cognitive function, and the clinical features of patients with Alzheimer's Disease, mild cognitive impairment, and subjective cognitive impairment (25). These investigators found that cognitive function assessed by a battery of neuropsychological tests varied in accordance with what would be expected over the

course of neurodegenerative disease progression. Moreover, cognitive decline significantly predicted cerebrospinal fluid amyloid b protein (AB_{42}) load and total tau protein, both indices of neurodegeneration and Alzheimer's Disease progression. Therefore, cognitive function is an important measure throughout the aging process due to its diagnostic and prognostic value concerning neurodegenerative disease.

Cognitive function has also been shown to be predictive of cardiovascular disease. In 2005, Elkins et al. conducted a prospective cohort study examining whether impaired cognitive function reflects an early manifestation of vascular injury in the brain and whether impaired cognitive function predicts the development of CVD (26). These investigators reported that lower scores of cognitive function were associated with a significant increase in the risk of cardiovascular events (e.g., myocardial infarction, death from CHD, and stroke) and the magnitude of the association was comparable to other established predictors of CVD risk including left ventricular hypertrophy on EKG and an HDL-C level < 35 mg/dL. A subsequent 2021 study supported this finding and found that a decrease per one standard deviation in a composite score of cognitive function and different cognitive function scores (e.g., immediate verbal recall and delayed verbal recall) resulted in a significant increase in risk of participants experiencing their first event of CVD (e.g., unstable angina pectoris, acute myocardial infarction, and stroke (27).

In addition to neurodegenerative and cardiovascular disease, cognitive function is associated with all-cause and cause-specific mortality in middle aged and older population (5, 28-32). In 2003, Pavlik et al. examined whether an inverse association between cognitive function and all-cause mortality exists in middle aged adults, similar to the association observed in older adults (28). Three measures of cognitive function were utilized which included the Digit

Symbol Substitution Test, Delayed Word Recall Test, and the Word Fluency Test. Following full adjustment, significant reductions in all-cause mortality risk were observed for every one-point score increment on the Delayed Word Recall Test and every seven-point score increment on the Digit Symbol Substitution Test. These investigators concluded that cognitive function is a robust predictor of all-cause mortality in middle-aged adults and cognitive function has important prognostic importance for life expectancy, like what has been observed in older adult populations.

A subsequent 2020 study examined the association between baseline cognitive function, cognitive transition, and all-cause mortality in community-dwelling older adults (≥ 65 years of age) (29). Cognitive function was assessed with the Mini-Mental State Examination and cognitive function was dichotomized as cognitive impairment and normal cognitive function, while accounting for education level. After a mean follow-up of 6.62 years, a two-fold increase in all-cause mortality risk was observed in participants with baseline cognitive impairment. These investigators also expanded on previous literature by examining cognitive transition in this population. Interestingly, individuals who reverted from impaired to normal and individuals whose cognitive function remained impaired over a one-year period exhibited an approximate three-fold and four-fold increase in all-cause mortality risk, respectively. No significant increases in all-cause mortality risk were observed in participants who had normal cognitive function at baseline. These results suggest that baseline cognitive function may exert a greater influence on mortality risk than cognitive transition over a one-year period.

When examining cause-specific mortality, a 2016 study examined the association between general cognitive function in middle and older age and the subsequent risk of death from chronic diseases (5). Cognitive function was assessed with a battery of neuropsychologic

tests which examined three domains of cognitive function including memory, executive function, and processing speed. Following nine years of follow-up, these investigators reported that for each one standard deviation decrease in cognitive function, there was a 49%, 13%, and 97% increase in the risk of CVD-related, cancer-related, and respiratory illness-related mortality, respectively. The association between cognitive function and CVD-related mortality was expanded on in a 2018 study conducted by An et al. (32). In adults ≥ 55 years at baseline, low cognitive function assessed with the Mini-Mental State Examination was associated with a significant increase in CVD-related mortality. These investigators reported that participants in the lowest quartile of cognitive function exhibited a 4.5-fold increase in CVD-related mortality risk and for every five-point decrease in Mini-Mental State Examination score, a 56% increase in CVD-related mortality was observed. Furthermore, low cognitive function has important prognostic value for cause-specific mortality in addition to all-cause mortality.

Social Support

Classic and current models of successful aging, such as those proposed by Young and colleagues and Rowe and Kahn, posit that social functioning (i.e., a multidimensional component which includes loneliness, social activity, instrumental support, and emotional support) is a key factor for healthy and successful aging (33, 34). This has been reflected in previous evidence, which has suggested an inverse association between social support and health-damaging behaviors including tobacco use, alcohol consumption, physical inactivity, and obesity (35). The association between social support and health-damaging behaviors subsequently elucidates an association between social support and CVD risk. In older adults ≥ 70 years of age, social isolation and low social support have been shown to be associated with a 66% and two-fold increase in CVD risk, respectively (36). The augmented CVD risk in individuals may be

attributed to social support's influence on CVD risk factors. In a 2006 cross-sectional study conducted by Hawkley et al. (37), an absence of social support (i.e., loneliness) was associated with elevated systolic blood pressure and age-related increases in systolic blood pressure in adults 50-68 years of age. Additionally, significantly greater coronary atherosclerosis has been reported in women (ages 30-65 years) with social isolation, in women who lacked emotional support, and in women who had a lack of interpersonal social relations (38). Therefore, both social support and lack of social support have important implications for health outcomes during the aging process.

In addition to cardiovascular health, social support has important implications for cognitive function throughout the aging process. The interactional brain hypothesis suggests that social interaction is a constitutive component in the development and operation of brain mechanisms, whether the individual is engaged in an interactive situation or not (39). In a 2021 systematic review of 22 studies, a positive association between social support and cognition was reported and the importance of social support was found to increase with age (40). During older adulthood, the researchers also found that emotional support (i.e., the provision and availability of esteem, trust, concern, listening, and love) and instrumental support (i.e., the provision of assistance with concrete needs, such as aid in money or labor) were two key dimensions in the relationship between social support and cognition (41). Therefore, the importance of functional social relationships (i.e., the social and emotional resources which are provided by others, or the perception of their provision) during older adulthood has been revealed (42).

In addition to the importance of functional social relationships during the aging process, the size of one's social support network has also been shown to influence cognitive function, revealing the importance of structural social relationships. Structural social relationships reflect

participation in a broad range of social relationships and refer to the quantitative characteristics of social relationships (42, 43). In 2004, Barnes et al. conducted a prospective cohort study to examine the association between social resources, cognitive function, and cognitive decline in older adults ≥ 65 years of age (44). Two measures were utilized to assess an individual's social resources, including social network size and social engagement. Social network size was based on the number of children, relatives, and friends the participant saw at least one a month, while social engagement was assessed with four items related to social and productive activity. These investigators reported that larger social network sizes and greater social engagement were positively correlated with baseline level of cognitive function ($P < 0.001$ for both). In addition, both social network size and social engagement were associated with an attenuated rate of cognitive decline. Individuals in the 90th percentile of social network size had a 39% reduction in the rate of cognitive decline when compared to participants in the 10th percentile of cognitive decline. Individuals with high social engagement reduced the rate of cognitive decline by 91%.

When examining older adults ages 80-98 years of age, similar findings were reported in a 2021 study which examined the associations between aspects of social engagement (i.e., social network size, social support, social isolation, and loneliness) and health outcomes (45). These investigators reported that larger social support network sizes were associated with better scores on a composite measure of cognition. These investigators concluded that larger social support networks provide greater opportunities for both social engagement and social support in older adulthood. Additionally, a 2017 systematic review of 39 studies found that larger social networks were associated with better levels of global cognition in adults ≥ 50 years of age (46). Therefore, these studies exemplify the importance of examining the association between structural social

relationships and cognitive function, as larger social networks have been shown to be associated with better cognitive function.

Therefore, the associations between social support (i.e., both functional and structural social relationships), health outcomes, and cognitive function has been established. However, social support also has important implications for mortality risk. In 2015, Becofsky et al. examined the associations between source of weekly social network, social support network size, and all-cause mortality risk (47). Following a median follow-up of 13.5 years, participants who reported social support from family and social support from a spouse/partner exhibited a 19% reduction in all-cause mortality risk ($P = 0.01$ for family social support; $P = 0.04$ for spouse/partner social support). When examining social support network size, participants who reported weekly contact with six or seven close friends exhibited a 24% reduction in all-cause mortality risk compared to participants in contact with zero or one friend. Therefore, these investigators concluded that both social support network size and source of social support have important health consequences related to mortality risk, exemplifying the importance of both structural and functional social relationships for attenuating mortality risk.

In 2013, Barger also examined the association of functional and structural social relationships with mortality (42). Using data from the U.S. National Health Interview Survey, a social integration variable was created using eight binary questions including four questions assessing the past two weeks contacts with relatives or friends, three questions assessing whether the participant attended a religious service, group social activity, or went out to eat, and one question assessing whether the participant was married or living with a partner. Social support was assessed with the question, “How often do you get the social and emotional support you need- always, usually, sometimes, rarely, or never?” Following five years of follow up, a 14%

reduction in all-cause mortality risk was observed in participants with the highest social integration. No significant reduction in all-cause mortality risk was observed in participants with the highest levels of social support. These investigators concluded that maintaining some degree of social relationship activity may be more important for mortality risk than the quality of the relationships.

A subsequent 2019 prospective cohort study expanded on these results and assessed the independent association between social integration and risks of all-cause and cause-specific mortality using data from the U.S. National Health Interview Survey (48). Social integration was determined using the same eight binary questions that Barger (2013) utilized. Following a mean follow-up of 13.8 years, a 30%, 33%, and 53% reduction in the risk of all-cause, CVD-related, and diabetes-related mortality were observed in participants with the highest level of social integration compared to participants with the least level of social integration, respectively. These investigators reported that the association between social integration and mortality risk was linear and consistent across age groups, sex, income, education, and employment status. By contrast, social support was not associated with all-cause or cause-specific mortality risk. These results supported the findings of Barger (2013) and expanded on them by examining cause-specific mortality. These investigators also reported that the association between social integration and CVD-related mortality may be explained by previous evidence, which found that individuals with higher levels of social integration were more likely to participate in leisure time physical activity, were less likely to smoke or more likely to quit smoking and had better adherence to a healthy lifestyle and medication compliance (49-51).

Two different mechanisms have been proposed which account for the association between social support and mortality risk including the stress buffering model and the main

effects model. The stress buffering model posits that social relationships moderate the deleterious influences of stress on health (52). This occurs as social relationships may provide resources which promote adaptive behavioral or neuroendocrine responses to either acute or chronic stressors. This has been observed as social support has been shown to be associated with reduced cortisol reactivity, diminished activity in the dorsal anterior cingulate cortex, and diminished activity in Brodmann's area 8 (i.e., two brain regions previously associated with the distress of social separation) (53). By contrast, low levels of social support have been associated with increases in heart rate, blood pressure, and exaggerated cardiovascular and neuroendocrine responses to laboratory stressors (54).

The main effects model differs from the stress buffering model in that the main effects model argues that social relationships are beneficial, regardless of an individual's stress level (55). The main effects model suggests that social relationships promote normative health behaviors and triggers positive psychological responses (i.e., feeling loved, sense of belonging, and security) which increase motivation to care for oneself, contentment, and favorable physiological reactions (56). Therefore, social relationships may directly encourage or indirectly model health behaviors (52). For example, social networks may influence whether individuals exercise, eat low-fat foods, or smoke (55). Therefore, it is social relationships which promote normative health behaviors and positive psychological responses, rather than the moderation of behavioral or neuroendocrine responses, which explain the association between social support and mortality.

Physical Activity

Physical activity is an important component of successful aging as physical activity reduces the risk of multiple chronic diseases including CVD, thromboembolic stroke,

hypertension, type 2 diabetes mellitus, osteoporosis, obesity, colon cancer, breast cancer, anxiety, and depression (57). Physical activity also contributes to the maintenance of activities of daily living throughout the aging process as physical activity reduces the risk of falls and injuries from falls, prevents functional limitations, and can function as a therapy for many chronic diseases. Because of the health benefits achieved with physical activity, physical activity guidelines for older adults have been established. The 2018 Physical Activity Guidelines for Americans recommend that older adults should perform 150-300 minutes per week of moderate-intensity physical activity or perform 75-150 minutes per week of vigorous-intensity physical activity with muscle-strengthening activities performed on at least two days per week (58). Additionally, the 2018 Physical Activity Guidelines recommended that older adults should engage in multicomponent physical activity such as balance training. Therefore, both performing and maintaining physical activity are important considerations for older adults in order to attenuate chronic disease risk, reduce fall risk, and maintain activities of daily living.

During the aging process, physical activity has also been shown to enhance existing cognitive function and prevent or delay the onset of cognitive decline. In 2008, Lautenschlager et al. conducted a randomized controlled trial to examine whether physical activity attenuates the rate of cognitive decline in adults (≥ 50 years of age) at risk for Alzheimer's Disease (12). Participants were randomly assigned to either a 24-week home based physical activity program (i.e., consisting of walking, aerobic exercise, and strength training) or to an education and usual care group. Cognitive function and cognitive decline were assessed using the cognitive section of the Alzheimer Disease Assessment Scale (ADAS-Cog). Following the 24-week intervention, participants who completed the physical activity intervention had significantly ($P = 0.04$) better ADAS-Cog scores when compared to participants in the education and usual care group. These

investigators also reported that the participants who completed the physical activity intervention improved an average 1.3 points on the ADAS-Cog compared to participants in the education and usual care group. This is noteworthy because this improvement is comparable to the 0.5 point improvement in the ADAS-Cog associated with the use of Donepezil (i.e., an acetylcholinesterase inhibitor used to improve cognitive function in individuals with Alzheimer's disease). Therefore, this study suggests that physical activity enhances cognitive function in older adults at risk for Alzheimer's Disease and the effect of physical activity on cognitive function is comparable to other pharmacological interventions.

While Lautenschlager et al. (2008) revealed that physical activity improves cognitive function in adults at risk for Alzheimer's Disease, physical activity has also been shown to improve cognitive function in healthy, older adults. In 2021, Carta et al. conducted a randomized controlled trial to examine whether physical activity is effective at improving cognitive function in older adults ($\geq$ 65 years of age) (59). Participants were randomly assigned to either a 12-week physical activity intervention (i.e., consisting of moderate-intensity aerobic exercises, anaerobic exercises, "life movements," strength, and balance) or a control condition (i.e., consisting of cultural and educational activities). Cognitive function was assessed with the Italian version of the Addenbrooke's Cognitive Examination Revised (ACE-R). Following the 12-week intervention, a significant ($P = 0.04$) improvement on the ACE-R total score was observed in participants who completed the physical activity intervention. By contrast, no significant improvements were observed in participants in the control condition. These investigators concluded that moderate-intensity physical activity is associated with improvements in cognitive function in healthy, older adults.

Therefore, physical activity has been shown to enhance existing cognitive function in both adults at risk for Alzheimer's Disease and healthy, older adults. However, physical activity also attenuates the risk of cognitive decline. In 2011, Sofi et al. conducted a meta-analysis of 15 prospective cohort studies examining the association between physical activity and cognitive decline in healthy participants without dementia (60). Fourteen of the studies analyzed older adults ≥ 65 years of age, while one study examined middle aged adults ages 35-55 years of age. These investigators reported that participants who reported engaging in high levels of physical activity had a 38% reduction in the risk of cognitive decline when compared to sedentary participants ($P < 0.00001$). Additionally, participants who engaged in low-to-moderate levels of physical activity had a 35% reduction in the risk of cognitive decline ($P < 0.00001$). Furthermore, this study elucidates the importance of physical activity for attenuating the risk of cognitive decline in healthy participants without neurodegenerative disease.

Moreover, the relationship between physical activity, cognitive function, and cognitive decline has been established in both adults at risk for Alzheimer's Disease and in healthy, older adults. However, physical activity is also important for the prevention of neurodegenerative disease including dementia and Alzheimer's Disease. A 2008 systematic review of 16 prospective cohort studies conducted by Hamer and Chida reported that participants in the highest category of physical activity exhibited a 28% and 45% reduction in the risk of dementia and Alzheimer's Disease, respectively (61). A subsequent 2015 meta-analysis of 10 prospective cohort studies supported the findings of Hamer and Chida (2008), reporting a 39% reduction in the risk of Alzheimer's Disease in physically active older adults compared to non-active older adults (62). Therefore, physical activity is very important behavior throughout the aging process

and during older adulthood due to its protective effects against dementia and Alzheimer's Disease.

Various mechanisms have been posited to account for the association between physical activity, cognitive function, cognitive decline, and the risk of neurodegenerative disease (63). Physical activity may improve cognitive function and attenuate cognitive decline through its actions to improve cortical connectivity, increase hippocampal volume, preserve gray matter volumes, and facilitate neuroplasticity. Physical activity may also modify vascular risk factors and reduce cerebrovascular burden. This has been observed through physical activity's actions to improve glucose intolerance, hypertension, hyperlipidemia, and obesity. When examining the association between physical activity and neurodegenerative disease, physical activity may also reduce the risk of neurodegenerative disease by augmenting the release of brain-derived neurotrophic factor and insulin-like growth factor 1.

Therefore, physical activity exerts protective effects against cognitive decline and neurodegenerative disease. However, physical activity has also been established as a protective factor against both all-cause and CVD-related mortality. A 2008 systematic review and meta-analysis of 24 studies reported that participants reporting the highest level of physical activity had a 35% reduction in CVD-related mortality and a 33% reduction in all-cause mortality when compared to the least active participants (64). These findings were supported by a 2009 meta-analysis of 38 studies which found a 31% reduction in all-cause mortality risk in participants reporting the highest level of physical activity when compared to the least active participants (65).

Moreover, current levels of physical activity have been shown to be protective against both all-cause and CVD-related mortality risk. However, changes in physical activity are also

important for attenuating mortality risk. In 2019, Mok et al. examined the associations of baseline and long-term changes in physical activity on all-cause, CVD-related, and cancer-related mortality in middle aged and older adults 40-79 years of age (66). Following a median follow up of 12.5 years, these investigators reported that for each 10 kJ/kg/day difference in baseline physical activity energy expenditure between individuals, a 30% reduction in all-cause mortality risk, a 31% reduction in CVD-related mortality risk, and a 17% reduction in cancer-related mortality risk was observed. These investigators additionally reported that each 1 kJ/kg/day/year increase in physical activity energy expenditure was associated with a 22% reduction in all-cause mortality risk, a 25% reduction in CVD-related mortality risk, and a 12% reduction in cancer-related mortality risk. Moreover, the attenuated risk associated with changes in physical activity energy expenditure occurred independent of baseline physical activity energy expenditure. Therefore, this study suggests that changes in physical activity, not only baseline physical activity levels, are important for reducing one's mortality risk and promoting longevity.

Summary

In summary, low cognitive function has been established as an isolated risk factor for both all-cause and CVD-related mortality. Because the association between cognitive function and mortality has been shown to be independent of CVD risk factors, it is important to identify lifestyle factors which may mediate this association. Currently, there is very limited evidence examining whether social support and physical activity mediate the association between cognitive function and mortality risk. Therefore, because social support and physical activity have been shown to be independently associated with both cognitive function and mortality risk, it is important to examine whether these factors mediate the association between cognitive function and mortality risk to promote longevity during the aging process.

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Chapter Three: Methodology

The purpose of this study is to examine the potential mediating effects of social support network size and physical activity on the association between cognitive function and all-cause and cardiovascular disease (CVD)-related mortality risk. This section provides the details on the methodology used to address the research question.

DATA COLLECTION

The National Health and Nutrition Examination Survey (NHANES) is a continuous program conducted by the National Center for Health Statistics (NCHS). The purpose of the NHANES is to collect data about the health, nutritional status, and health behaviors of the non-institutionalized civilian population of the U.S. Findings from the NHANES are used to determine the prevalence of major diseases and risk factors for diseases, to assess nutritional status and its association with health promotion and disease prevention, and to establish national standards for measurements such as height, weight, and blood pressure (1). The study sample included 2,550 men and women (≥ 60 years of age) who participated in the 1999-2002 NHANES. Inclusion criteria for the sample included adults ≥ 60 years of age, individuals who attended the mobile examination center, women who were not pregnant, and individuals who completed data on all variables of interest.

PRIMARY DEPENDENT VARIABLE

The primary dependent variables in this study were all-cause mortality and CVD-related mortality. All-cause mortality was defined as death from all causes, while CVD-related mortality was defined as death from any disease of the heart. The NCHS linked death records from the National Death Index to the NHANES participants sequence numbers was utilized and mortality status was determined for sample participants.

PRIMARY INDEPENDENT VARIABLES

The primary independent variables in this study included cognitive function, social support network size, and total physical activity volume (TPAV). Cognitive function was assessed with the Digit Symbol Substitution Test (DSST) during the household interview of NHANES participants. The DSST is a component of the Weschler Adult Intelligence Test which assesses response speed, sustained attention, visual spatial skills, associative learning, and memory (2, 3). The DSST requires participants to copy symbols which are paired with numbers during a period of two minutes (3). Following the two-minute period, participants are scored based on the number of correct symbols drawn during the time limit. Two files were utilized to assess cognitive function within the NHANES. Cognitive Functioning Questionnaire File CFDRIGHT indicated the number correct on the DSST and Cognitive Functioning Questionnaire File CFD050 indicated DSST exercise completion. Quartiles of cognitive function were created based on DSST completion and the number correct: < 34 correct, 34-46 correct, 47-57 correct, and ≥ 58 correct.

Within NHANES, social support was assessed with questions from the Yale Health and Aging Study and the Social Network Index – Alameda County Study during the household interview. Social support network size was determined through the self-reported number of close friends. The Social Support Questionnaire File SSQ060 was utilized to assess social support network size. Social Support Questionnaire File SSQ060 asks participants, *"In general, how many close friends do you have? By "close friends" I mean relatives or non-relatives that you feel at ease with, can talk to about private matters, and can call on for help."* Three categories of social support were created: 0 reported close friends, 1-4 reported close friends, and ≥ 5 reported close friends.

TPAV was determined based on weekly MET values of aerobic physical activity across three physical activity domains (4). Two files in NHANES were utilized to create this variable. The Physical Activity Questionnaire file includes questions related to the frequency, intensity, and duration of transportation and domestic physical activity performed over the past 30 days. The Physical Activity Individual Activities Questionnaire file includes more detailed information about specific moderate and vigorous leisure-time physical activity. Using the Compendium of Physical Activity, MET values were assigned to each type of activity. Next, the average duration (minutes per session) was multiplied by the average frequency (number of sessions per week) and the intensity level (MET-level) to generate MET-minutes per week for each activity. MET-minutes per week were then summed for each domain of physical activity, resulting in the TPAV variable. Quartiles of TPAV were subsequently created which included ≤ 249 MET-minutes/week, 250-755 MET-minutes/week, 756-1,000 MET-minutes/week, and > 1,000 MET-minutes/week.

OTHER INDEPENDENT VARIABLES

Other variables were controlled for in this study to prevent any potential confounding. These variables included:

AGE

Age was dichotomized as 60-70 years of age and > 70 years of age.

EDUCATION

Education was divided into three categories which included less than high school, high school graduate, and more than high school.

RACE

Race was divided into four categories which included non-Hispanic white, non-Hispanic Black, Mexican American, and other including multi-racial and other Hispanic.

BLOOD PRESSURE

Blood pressure was divided into four categories based on the 2017 American College of Cardiology and American Heart Association Guidelines as: normal SBP < 120 mmHg and DBP < 80 mmHg, elevated SBP 120-129 mmHg and DBP < 80 mmHg, Stage 1 Hypertension SBP 130-139 mmHg and DBP 80-89 mmHg, and Stage 2 Hypertension SBP ≥ 140 mmHg and DBP ≥ 90 mmHg (5). Stage 1 and Stage 2 Hypertension were also based on responses to Blood Pressure & Cholesterol Questionnaire File BPQ050a, "Now taking prescribed medicine for high blood pressure."

WAIST CIRCUMFERENCE

Waist circumference was dichotomized based on the U.S. Department of Health and Human Services classifications of overweight and obesity (6). An elevated waist circumference was defined as ≥ 102 cm and ≥ 88 cm for men and women, respectively.

GLYCOHEMOGLOBIN

Glycohemoglobin was divided into three categories based on recommendations by the American Diabetes Association which included < 5.7%, 5.7-6.4%, and ≥ 6.5% (7).

SERUM COTININE

Tobacco use was dichotomized based on serum cotinine levels where a serum cotinine level < 3 ng/mL represented non-smoking level and a serum cotinine level ≥ 3 mg/mL indicated current tobacco use or current exposure (8).

STATISTICAL ANALYSIS

The data in this study was managed using SAS (Version 9.4; SAS Institute, Inc., Cary, NC) (9). SAS was used to conduct complex variable recording, data coding validation, and to conduct the analysis incorporating sampling weights within the context of the correlated multi-stage complex design inherent to the NHANES. Descriptive characteristics were obtained with the means (PROC SURVEYMEANS) and frequency (PROC SURVEYFREQ) procedures for continuous and categorical variables, respectively.

Cox proportional hazards regression analysis was performed with the PROC SURVEYPHREG procedure to determine whether social support network size and TPAV mediate the risk of all-cause and CVD-related mortality according to quartile of cognitive function. A forward selection process based on the results of the Cox proportional hazards regression analysis was used to generate three models for analysis. These included a crude Model 1, Model 2 adjusted for select demographic factors including sex, education, race, and age, and Model 3 adjusted for Model 2 covariates and blood pressure, smoking status, waist circumference, and glycohemoglobin.

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Chapter Four: Manuscript

THE POTENTIAL MEDIATING EFFECTS OF SOCIAL SUPPORT NETWORK SIZE AND PHYSICAL ACTIVITY ON COGNITIVE FUNCTION AND MORTALITY RISK

Abstract

BACKGROUND: Low cognitive function has been shown to be an independent predictor of all-cause and cardiovascular disease (CVD)-related mortality. Social support network size and total physical activity volume (TPAV) are two modifiable factors which have been shown to be independently associated with cognitive function and mortality risk. Therefore, the purpose of this study was to examine the potential mediating effects of social support network size and TPAV on cognitive function and all-cause and CVD-related mortality risk in a large, nationally representative sample of U.S. adults.

METHODS: Study sample (N =2,550) included older adult (≥ 60 years of age) participants in the 1999-2002 National Health and Nutrition Examination Survey. Quartiles of cognitive function were created using Digit Symbol Substitution Test scores. Social support network size was determined using the number of reported close friends. TPAV was determined from self-reported domestic, transportation, and leisure time physical activity.

RESULTS: Regression analysis revealed an approximate three-fold increase in all-cause and CVD-related mortality risk in participants in the lowest quartile of cognitive function, compared to the highest quartile of cognitive function. These relationships are independent of social support network size and TPAV. Linear and non-linear inverse dose-response relationships were also revealed between cognitive function and increased all-cause and CVD-related mortality risk, respectively (P for trend for both $P < 0.0001$).

CONCLUSION: In a large, nationally representative sample of U.S. older adults, low cognitive function was associated with increased all-cause and CVD-related mortality risk. However, both relationships were independent of social support network size and TPAV.

Introduction

Changes in cognitive function, including declines in speed of processing, working memory, and executive function, are part of the normal aging process (1). In the brain, structural and functional changes occur which account for these age-related changes, including loss of synapses, dysfunction of neuronal networks, and alterations in neuronal structure without neuronal death. Various factors such as cerebral ischemia, head trauma, toxin exposure, or excess stress hormones can cause damage to the brain throughout the aging process and produce cognitive impairments leading to declines in cognitive function.

Declines in cognitive function often occur in individuals ages 65-85 years of age and maintaining cognitive function in older adulthood has important implications for longevity (2). Cognitive function has been shown to be predictive of all-cause and cardiovascular disease (CVD)-related mortality in middle-aged and older populations (3-6). Low cognitive function has also been shown to be associated with increased all-cause mortality risk independent of several CVD-related biomarkers (i.e., elevated mean arterial pressure, high-sensitivity C-reactive protein, high density lipoprotein-cholesterol [HDL-C], total cholesterol, glycosylated hemoglobin [HbA1c], and body mass index) in older adults (4). Changes in cognitive function have also been shown to influence mortality risk as a decline in cognitive ability has been shown to be predictive of all-cause mortality independent of depression and other risk factors (3).

Collectively, this previous evidence has established cognitive function as an independent predictor of mortality. The likelihood of low cognitive function and cognitive decline is more common in an aging population (7). Globally, the population of adults aged 65 years and older is growing at a rapid rate (8). By 2050, it is projected that one in six people in the world will be over the age of 65 and the number of persons 80 years and older is projected to triple from 143

million in 2019 to 426 million in 2050. Consequently, the importance of identifying factors that may mediate the relationship between cognitive function and mortality risk remains an important research area due to the rapid growth of the older adult population across the globe.

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles which results in energy expenditure (9). Physical activity has been shown to be independently associated with both cognitive function and mortality risk (10, 11). Physical activity has been posited to attenuate cognitive decline through its actions to raise HDL-C, lower systolic blood pressure, and generally reduce CVD-related risk (10). In older adults, PA has been shown to be inversely associated with all-cause mortality risk (11). Physical activity has been suggested to reduce mortality risk through both physiological and behavioral mechanisms, including improved fibrinolytic activity, hemostatic function, glucose tolerance, lipid profile, blood pressure, inflammation, and oxidative stress (10). Physical activity may also attenuate mortality risk through actions that promote improved coping with stressful life events and reduce depression. Therefore, due to the beneficial impact of increased PA on both cognitive function and mortality risk, PA may be an important mediator of the association between cognitive function and mortality risk.

Social relationships are another factor which have been shown to be independently and beneficially associated with both cognitive function and mortality (12-14). Social relationships can be defined as either functional or structural. Functional social relationships (e.g., social support) have been defined as the social and emotional resources that people have or perceive as available to them, while structural social relationships (e.g., social support network size, social integration) reflect the quantitative characteristics of social relationships and refer to participation in a broad range of social relationships (15). A positive association between social

support network size and cognitive function has been reported in older adults, illustrating the importance of structural social relationships (15-17). Functional social relationships also influence cognitive function as social support has been linked to better cognitive functioning and less cognitive decline (12, 19-20). In older adults, greater baseline emotional support has been shown to be a significant predictor of better cognitive function over 7.5 years of follow up (12).

The interactional brain hypothesis has been proposed to account for the beneficial association between social support and cognitive function. This hypothesis suggests that interactions with others are a fundamental component of brain development and cognitive processes (21). Moreover, social interaction has been proposed to play a crucial role in the emergence of cognition, as observed with processes shaped by cultural rather than genetic evolution (e.g., imitation, mentalizing, and language) (22).

Functional and structural social relationships also have important implications for mortality risk. In a meta-analysis of 50 studies examining the associations between social support and all-cause mortality risk, it has been reported that individuals with lower levels of social support exhibited a significant increase in all-cause mortality risk (13). However, mortality risk is attenuated in individuals with greater levels of social support. It has been found that participants who reported social support from family and social support from a spouse/partner exhibited significant reductions in all-cause mortality risk, illustrating the importance of functional social relationships (23).

While the presence of social support (i.e., functional social relationships) has been shown to attenuate mortality risk, evidence suggests that social integration (i.e., structural social relationships) may exert a greater protective effect. When examining the association of functional and structural social relationships with mortality risk, it has been reported that social

integration (i.e., a measure of structural social relationships) is associated with a significant reduction in all-cause and cause-specific mortality risk, while the same association was not observed for social support (i.e., a measure of functional social relationships) (15, 24). Therefore, while both functional and structural social relationships have important implications for mortality risk, structural social relationships may be a stronger predictor of mortality.

Moreover, PA and social relationships have been shown to be associated with both cognitive function and mortality independently (10-13). However, there is limited evidence examining whether PA or social support network size mediate the relationship between cognitive function and mortality risk. Accordingly, the purpose of this study was to examine the potential mediating effects of social support network size and total PA volume (TPAV) on cognitive function and all-cause and CVD-related mortality risk in a large, nationally representative sample of U.S. older adults. It was hypothesized that social support network size and TPAV mediate the relationship between cognitive function and mortality risk, due to the independent associations between the variables (10-13).

Methods

Study Population

This study utilized four years of data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES). The NHANES is a continuous survey conducted by the National Center for Health Statistics (NCHS) which combines personal interviews with standardized physical examinations and laboratory tests (25). The NHANES collects data about the health, nutritional status, and health behaviors of the non-institutionalized population of the U.S. (0 months and older) (26). The NHANES uses a complex, multistage probability sampling

design to obtain a representative sample of the U.S. population. Participants in this study completed an informed consent and met the following inclusion criteria: were ≥ 60 years of age, attended the mobile examination center, were not pregnant, and individuals with complete data on all variables of interest. The final sample included 2,550 U.S. adults ≥ 60 years of age.

Cognitive Function

Cognitive function was assessed using the Digit Symbol Substitution Test (DSST). The DSST is a component of the Wechsler Adult Intelligence Scale (WAIS) and requires response speed, sustained attention, visual spatial skills, associative learning, and memory (27). The DSST is a valid and sensitive measure of cognitive dysfunction which is impacted by several domains. Performance on the DSST correlates with functional outcomes (i.e., ability to perform activities of daily living) and recovery from functional disability in various psychiatric conditions (e.g., schizophrenia and major depressive disorder). Within the NHANES, the DSST was chosen as a measure of cognitive function because it may be a more sensitive measure of cognitive function than the Mini-Mental State Examination (MMSE) and it has also been previously administered in the National Institute on Aging's Health ABC study (28, 29).

The DSST testing protocol requires participants to copy symbols which are paired with numbers during a period of two minutes (27). The initial duration of the DSST was 90 seconds. However, this duration was increased to two minutes with the creation of the third edition of the WAIS. Following the two-minute testing period, participants are scored based on the number of correct symbols successfully drawn during the time limit. Quartiles of cognitive function were created based on the number correct: < 34 correct, 34-46 correct, 47-57 correct, and ≥ 58 correct.

Total Physical Activity Volume

Total PA volume was determined based on weekly metabolic equivalent (MET) values for aerobic PA across three domains (i.e., leisure-time PA [LTPA], transportation PA, and domestic PA) (30). First, the frequency, intensity, and duration of transportation and domestic PA performed over the past 30 days was determined for each participant. The Compendium of PA MET values were then assigned to each type of activity (31). The average duration (minutes per session) was then multiplied by the average frequency (number of sessions per week) and the intensity level (MET-level) to create MET-minutes per week for each activity. MET-minutes per week were summed for each domain of PA to create the TPAV variable. Quartiles of TPAV included ≤ 249 MET-minutes/week, 250-755 MET-minutes/week, 756-1,000 MET-minutes/week, and > 1,000 MET-minutes/week.

Social Support Network Size

The social support portion of the NHANES was conducted during the household interview using questions selected from the Yale Health and Aging Study and the Social Network Index – Alameda County Study (32). Social support network size was determined using the question, "*In general, how many close friends do you have? By "close friends" I mean relatives or non-relatives that you feel at ease with, can talk to about private matters, and can call on for help*" (12, 33-34). Three categories of social support were created: none, 1-4, and ≥ 5 close friends.

Covariates

Age was dichotomized as 60-70 years of age and > 70 years of age. Three categories of education were used which included less than high school, high school graduate, and more than high school. Four categories of race/ethnicity were utilized which included non-Hispanic white,

non-Hispanic Black, Mexican American, and other including multi-racial and other Hispanic. Blood pressure was divided into four categories based upon the 2017 American College of Cardiology and American Heart Association guidelines: normal (SBP [Systolic Blood Pressure] ≤ 120 mmHg and DBP [Diastolic Blood Pressure] ≤ 80 mmHg), elevated (SBP 120-129 mmHg and DBP ≤ 80 mmHg), Stage 1 Hypertension (SBP 130-139 mmHg and DBP 80-89 mmHg) and Stage 2 Hypertension (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg) (35). Waist circumference (WC) was dichotomized based on the 2013 Systematic Evidence Review from the Obesity Expert Panel (36). Waist circumference was categorized as elevated at ≥ 102 cm and ≥ 88 cm, for men and women, respectively. The three categories of HbA1c analyzed were based on recommendations by the American Diabetes Association which included < 5.7%, 5.7-6.4%, and ≥ 6.5% (37). Active smoking and environmental tobacco smoke exposure was assessed with serum cotinine levels, a metabolite of nicotine. Serum cotinine levels were dichotomized based on having a serum cotinine level ≥ 3 ng/mL (38).

Mortality

The dependent variables in this study were all-cause and CVD-related mortality. The NCHS linked death records from the National Death Index to the 1999-2002 NHANES participants using a process outlined elsewhere (39). The cause of death was determined and classified by the International Statistical Classification of Diseases, Injuries, and Causes of Death-10 codes for participants who were identified as deceased. All-cause mortality was defined as death from all causes, while CVD-related mortality only included death from diseases related to the heart.

Statistical Analysis

The data in this study was managed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC) (40). SAS was utilized to conduct complex variable recodes, data coding validation, and to conduct the analysis incorporating sampling weights within the context of the correlated multi-stage complex design inherent to the NHANES. Mean (PROC SURVEYMEANS) and frequency (PROC SURVEYFREQ) procedures were used to generate descriptive statistics for continuous and categorical variables, respectively. Cox proportional hazards regression analyses were performed using the PROC SURVEYPHREG procedure. The models analyzed included a crude Model 1, Model 2 adjusted for demographic factors including age, race/ethnicity, sex, and education, and a fully-adjusted Model 3 adjusted for Model 2 covariates, blood pressure, serum cotinine, WC, and HbA1c.

Results

The study characteristics of the participants according to quartiles of cognitive function are summarized in Table 1. The mean age of participants in the highest quartile of cognitive function was significantly ($P < 0.05$) lower than the mean age of participants in the other three quartiles of cognitive function. The greatest proportion of female participants was also found in the highest quartile of cognitive function. While 9.5% of the participants in the highest quartile of cognitive function had less than a high school education, 70.3% of participants in the lowest quartile of cognitive function had less than a high school education. Participants in the highest quartile of cognitive function also had significantly ($P < 0.05$) lower mean HbA1c levels when compared to participants in the lowest quartile of cognitive function.

Table 1. Study Characteristics of U.S. Adults ≥ 60 years of age: NHANES 1999-2002 (N=2,550).

	Point Estimate (95% CI)			
	Cognitive Function Quartile 1	Cognitive Function Quartile 2	Cognitive Function Quartile 3	Cognitive Function Quartile 4
N, % of total sample	875 (34.3)	649 (25.5)	500 (19.6)	526 (20.6)
Age, mean, years	73.9 (73.0-74.9)	71.7 (71.1-72.4)	70.0 (69.1-70.9)	67.0 (66.4-67.6)
Gender, % female	45.8	48.5	54.6	58.9
Race-ethnicity, % nH white	39.5	61.6	72.4	81.0
Education, % less than high school	70.3	38.2	20	9.5
Elevated serum cotinine concentration, %	17.9	16.2	14.2	11.6
Waist Circumference, mean, cm				
Men	102.1 (100.6-103.6)	105.1 (103.5-106.7)	105.1 (103.1-107.0)	103.8 (102.5-105.1)
Women	97.4 (95.5-99.2)	96.0 (94.5-97.5)	97.6 (95.8-99.5)	94.8 (93.2-96.3)
Glycohemoglobin, mean %	5.95 (5.82-6.08)	5.92 (5.81-6.04)	5.74 (5.63-5.85)	5.59 (5.52-5.67)
DSST, mean, number correct	23.6 (22.8-24.5)	40.1 (39.8-40.3)	52.2 (51.8-52.5)	68.0 (67.4-68.5)
Total Weekly Physical Activity Volume, % in lowest quartile of TPAV	66.5	57.5	47.8	41.3
Network Size, close friends, %				
0	6.7	3.7	4.0	1.2
1-4	45.3	34.8	28.6	28.1
≥ 5	48.0	61.5	67.4	70.7

Results of the Cox proportional hazards regression analysis examining the potential mediating effects of TPAV and social support network size on all-cause mortality risk are shown in Table 2. Crude analysis revealed a significant increase in all-cause mortality risk in the three lowest quartiles of cognitive function, independent of social support network size and TPAV. An approximate 3.5-fold ($P < 0.0001$) increase in all-cause mortality risk was observed in participants in the lowest quartile of cognitive function when compared to a referent group with participants in the highest quartile of cognitive function. A 2.6-fold ($P < 0.0001$) and 1.7-fold ($P < 0.01$) increase in all-cause mortality risk was observed in participants in the second quartile of cognitive function and in participants in the third quartile of cognitive function, respectively. After adjusting for select demographic factors including sex, education, race/ethnicity, and age, all-cause mortality risk was slightly attenuated but remained significant in participants in the three lowest quartiles of cognitive function, independent of social support network size and TPAV. After full adjustment for metabolic and lifestyle risk factors, a significant increase in all-cause mortality risk was maintained in participants in the three lowest quartiles of cognitive function, regardless of social support network size and TPAV. An approximate three-fold ($P < 0.0001$) increase in all-cause mortality risk was observed in participants in the lowest quartile of cognitive function, while participants in the second quartile of cognitive function exhibited a two-fold ($P < 0.0001$) increase in all-cause mortality risk. A linear inverse dose-response relationship was also revealed between low cognitive function and increased all-cause mortality risk ($P < 0.0001$ for trend).

Table 2. Potential Mediating Effects of TPAV and Social Support on All-Cause Mortality Risk

	Model 1 HR[a] (95% CI)	Model 2 HR[b] (95% CI)	Model 3 HR[c] (95% CI)
Cognitive Function Group 1	3.57 (2.97-4.30)*	2.93 (2.38-3.61)*	2.89 (2.33-3.59)*
Cognitive Function Group 2	2.60 (1.99-3.38)*	2.05 (1.57-2.69)*	2.06 (1.57-2.71)*
Cognitive Function Group 3	1.69 (1.32-2.17)**	1.44 (1.14-1.82)**	1.39 (1.09-1.78)**
Cognitive Function Group 4	1.00	1.00	1.00

[a] Unadjusted crude model.

[b] Adjusted for gender, education, race, and age.

[c] Adjusted for gender, education, race, age, blood pressure, smoking status, waist circumference, and glycohemoglobin.

*$P < 0.0001$

**$P < 0.01$

Table 3 illustrates the results of the Cox proportional hazards regression analysis examining the potential mediating effects of TPAV and social support network size on CVD-related mortality risk. Crude analysis revealed a significant increase in CVD-related mortality risk in participants in the two lowest quartiles of cognitive function, independent of social support network size and TPAV. An approximate three-fold and 2.4-fold ($P < 0.01$ for both) increase in CVD-related mortality risk was observed in participants in the lowest quartile of cognitive function and in participants in the second quartile of cognitive function, respectively. However, no significant increase in CVD-related mortality risk was observed in participants in the third quartile of cognitive function. A slight reduction in CVD-related mortality was observed in these participants, however, the hazards ratio failed to reach statistical significance.

After adjusting for select demographic factors (i.e., sex, education, race/ethnicity, and age), the relationship was slightly attenuated but remained significant in participants in the lowest quartile of cognitive function and in the second quartile of cognitive function. Similar to the crude analysis, the relationship between cognitive function and CVD-related mortality was not mediated by social support network size or TPAV. Following full adjustment for metabolic and lifestyle risk factors, CVD-related mortality risk remained significant in participants in the lowest quartile of cognitive function and in the second quartile of cognitive function, independent of social support network size and TPAV ($P < 0.01$ for both). No significant increases in CVD-related mortality risk were observed in participants in the third quartile of cognitive function when compared to the highest quartile of cognitive function. A non-linear inverse dose-response relationship was revealed between low cognitive function and increased CVD-related mortality risk ($P = 0.0002$).

Table 3. Potential Mediating Effects of TPAV and Social Support on CVD-Related Mortality Risk

	Model 1 HR[a] (95% CI)	Model 2 HR[b] (95% CI)	Model 3 HR[c] (95% CI)
Cognitive Function Group 1	2.96 (1.77-4.95)**	2.83 (1.61-4.99)**	2.67 (1.54-4.64)**
Cognitive Function Group 2	2.42 (1.42-4.13)**	2.18 (1.23-3.89)**	2.05 (1.21-3.49)**
Cognitive Function Group 3	0.90 (0.45-1.81)	0.82 (0.38-1.77)	0.78 (0.39-1.57)
Cognitive Function Group 4	1.00	1.00	1.00

[a] Unadjusted crude model.

[b] Adjusted for gender, education, race, and age.

[c] Adjusted for gender, education, race, age, blood pressure, smoking status, waist circumference, and glycohemoglobin.

**$P < 0.01$

Discussion

Our findings suggest that low cognitive function is associated with a significant increase in all-cause and CVD-related mortality risk, independent of TPAV and social support network size. To our knowledge, this is the first study to examine whether social support network size and TPAV mediate the relationship between cognitive function and mortality risk. This is also the first to our knowledge that examines this relationship in a large and nationally representative sample of the U.S. population.

In the present study, a significant increase in all-cause mortality risk was observed for every quartile of cognitive function when compared to a referent group with the highest cognitive function score (DSST score ≥ 58 correct), independent of social support network size and TPAV. However, a significant increase in CVD-related mortality was only observed for individuals in the first and second quartiles of cognitive function. This suggests that the mechanisms relating cognitive function to an augmented mortality risk may differ based on cause of death.

Differences in the association between cognitive function and mortality risk based on cause of death have been reported (41, 42). In a 2018 prospective cohort study conducted by An et al. examining the association between MMSE-assessed cognitive impairment and the risk of all-cause and CVD-related mortality, the association between cognitive function and mortality differed based on the type of mortality examined (41). Following full adjustment (i.e., including exercise and marital status), these investigators reported a significant increase in CVD-related mortality risk in participants in all quartiles of cognitive function when compared to a referent group with the highest cognitive function (MMSE score 28-30). However, a significant increase in all-cause mortality risk was only observed in participants in the first and second quartiles of

cognitive function. Similar results were reported in a subsequent 2020 study conducted by Tamosiunas et al. (6) who found that the risk of all-cause mortality was less significant compared to CVD-related mortality and in a 2016 study conducted by Batty et al. (42) who reported that the strength of the association between cognitive function and mortality differed based on cause (i.e., cancer mortality, CVD-related mortality, respiratory illness mortality, and other causes).

These differences may be due in-part to differences in the populations analyzed, and the assessments of cognitive function utilized. For example, An et al. (41) examined adults ≥ 55 years of age from the Beijing Longitudinal Study of Aging and Tamosiunas et al. (6) examined adults 45-72 years of age from the Health, Alcohol, and Psychosocial Factors in Eastern Europe study. The present study examined adults ≥ 60 years of age from the NHANES. Additionally, An et al. (41) used the MMSE to assess cognitive function, while the present study used the DSST. The MMSE is an index of global cognitive function, while the DSST assesses components of executive function (i.e., response speed, sustained attention, visual spatial skills, associative learning, and memory) (27). Some evidence suggests that executive function may be a stronger predictor of mortality when compared to global cognitive function (43, 44).

The present study suggests that low cognitive function is an independent predictor of all-cause and CVD-related mortality, independent of social support network size. In 2009, Obisesan and Gillum examined the independent effects of structural social relationships (i.e., social integration) and cognitive function on mortality risk in older adult participants (≥ 60 years of age) in the third NHANES (45). Cognitive function was assessed with a short index of cognitive function (SICF), which consisted of subsets of different cognitive screening instruments including the MMSE, Short Portable Mental Status Questionnaire, and Weschler Adult Intelligence Scale. Overall scores were determined for participants and quartiles of cognitive

function were utilized. Structural social relationships were assessed using a social network index comprising of marital status, frequency of contacts in domains of friends and relatives, religious attendance, and voluntary associations. The social network index score ranged from 0-4 and three categories were examined (i.e., 0-1, 2, and 3-4).

Following an average follow-up of 8.5 years, these investigators reported that mortality risk was higher in those in the lowest quartile of cognitive function when compared to those in the highest quartile of cognitive function, and in those with the lowest social integration index compared to those with the highest social integration index. However, a significant interaction between SICF score and structural social relationships was not revealed. This finding was similar to the results of the present study as low cognitive function was associated an increased mortality risk independent of structural social relationships (i.e., social support network size), indicating that no interaction occurred between the two variables. Moreover, while structural social relationships may be independently associated with cognitive function and mortality risk, they do not mediate the association between these two variables based on the results of this study.

Subsequently, in 2010, Gillum and Obisesan examined how LTPA may modify the effect of cognitive function on mortality risk in older adult participants in the third NHANES (10). These investigators reported that both low cognitive function and a low LTPA volume were independently associated with increased mortality risk. However, an interaction between cognitive function and LTPA was not revealed, similar to the results of the present study. Moreover, these previous studies support the evidence suggesting that cognitive function, social relationhips, and PA relate to mortality risk independently. However, structural social relationships and TPAV may be insufficient to account for the relationship between cognitive function and mortality.

Overall, the mechanisms relating low cognitive function to increased mortality risk remain unclear. However, other possible mechanisms relating low cognitive function to an increased mortality risk have been suggested. First, the relationship between cognitive function and mortality risk may be explained by health literacy (6). Health literacy has been defined as the skills required to access and synthesize health information and has been shown to be directly associated with cognitive function (46). Health literacy relates to mortality as individuals with low cognitive function and low health literacy may be less likely to seek appropriate medical care and health information concerning the promotion and maintenance of good health (2). Therefore, health literacy may be an important component for promoting longevity which may be attenuated in individuals with low cognitive function.

Second, cognitive function may influence health and mortality risk through a multi-dimensional concept like frailty. Frailty is characterized by weight loss, exhaustion, weakness, slow walking speed, and physical inactivity (47). Frailty has been shown to be directly associated with cognitive impairment and frail elderly adults have been shown to be eight times more likely to develop cognitive impairment, six times more likely to develop vascular dementia, and four times more likely to develop dementia due to Alzheimer's Disease.

The phenomenon of cognitive frailty has also recently been proposed. Cognitive frailty has been characterized as a syndrome in older adults who develop both cognitive impairment (i.e., without a clinical diagnosis of Alzheimer's Disease or another dementia) and physical frailty (48). Cognitive frailty also has implications for mortality risk. In a 2020 systematic review and meta-analysis, a two-fold increase in all-cause mortality risk was observed in cognitively frail individuals when compared to older adults without cognitive frailty (49). Lastly, low cognitive function may be related to an increased mortality risk due to the beginning processes of

the pathophysiology of dementia including vascular mechanisms such as micro-infarcts, micro-hemorrhages, strategic white matter tracts, loss of microstructural tissue integrity, and neurodegeneration (50, 51).

Our results suggest that low cognitive function is associated with increased all-cause and CVD-related mortality risk, independent of TPAV and social support network size. This finding is in contrast with the proposed hypothesis suggesting that social support network size and TPAV mediate the relationship between cognitive function and mortality risk. However, the results of this study do suggest the importance of maintaining cognitive function throughout the aging process and into older adulthood to promote longevity. The results of this study also suggest that the DSST may be an important tool to use throughout the aging process due to the prognostic value of DSST assessed cognitive function.

The present study is not without limitations. First, the use and operationalization of social relationships was limited secondary to the nature of the NHANES. Within the NHANES, participants are asked questions regarding whether they have anyone to help with emotional support and who provides emotional support. Participants are also asked whether they needed more emotional support in the past year. Lastly, participants are asked to report their number of close friends. Due to the paucity of questions asked within the NHANES related to social relationships, the self-reported number of close friends was chosen as an indicator of structural social relationships. However, a more global measure of social relationships may provide greater insight into the association between social relationships, cognitive function, and mortality risk. Limitations of the present study also include the inability to track potential changes in cognitive function between initial measurement and death. Additionally, causality cannot be established due to the cross-sectional design of the study. A major strength of our study is the contribution

that our findings make to the limited evidence examining whether social support network size and TPAV mediate the relationship between cognitive function and mortality risk. Secondly, the NHANES is a large, population-based, and nationally representative sample which allows results to be generalized to the older U.S. adult population. Lastly, cognitive function was objectively measured, which minimizes the effects of recall and reporting biases.

Conclusion

In a large, nationally representative sample of older adults, low cognitive function was associated with an increased risk of all-cause and CVD-related mortality, independent of social support network size and TPAV. These results support the importance of maintaining cognitive function throughout the aging process to attenuate both all-cause and CVD-related mortality risk. These results also provide support for clinicians utilizing the DSST, a measure of executive function, to assess mortality risk in older adults.

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Appendices

Appendix A: JOINT EFFECT OF COGNITIVE FUNCTION AND C-REACTIVE PROTEIN ON ALL-CAUSE MORTALITY RISK: 1999-2002 NHANES

Abstract

Purpose: Examine the joint effect of cognitive function and C-reactive protein (CRP) on all-cause mortality risk in older U.S. adults.

Methods: Sample included 1,335 older adult (≥ 60 years of age) participants in the 1999-2002 National Health and Nutrition Examination Survey. A four-level variable was created using cognitive function and CRP concentration. Mortality was assessed using National Center for Health Statistics linked death records from the National Death Index.

Results: Increased risk of all-cause mortality was revealed in adults with high CRP and low cognitive function and in those with low to average CRP and low cognitive function ($P < 0.0001$ for both). The joint effect of cognitive function and CRP on all-cause mortality risk differed according to sex.

Conclusion: Low cognitive function was associated with increased all-cause mortality risk independent of CRP concentration. Sex-stratified analyses revealed increased all-cause mortality risk in males with low cognitive function, independent of CRP concentration. However, in females, a significant increase in all-cause mortality risk was only observed in those with low to average CRP and low cognitive function.

Introduction

"Inflammaging" is characterized as a state of chronic low-grade inflammation, which is associated with a significant increase in risk of morbidity and mortality in older populations (1). C-reactive protein (CRP) is a non-specific biomarker for systemic inflammation and has been shown to be related to the development of atherosclerosis and an increased risk of cardiovascular disease (CVD)- related events and mortality (2-5). Elevated CRP is also associated with an increased risk of cognitive decline (6-8), disability in activities of daily living, and reduced functional capacity (9). In the brain, central inflammation results in synaptic remodeling, neuronal apoptosis, and impaired neurogenesis which disrupts hypothalamic function and impairs the outputs necessary for effective cognitive function (10).

Low cognitive function has been shown to be linked to an increased mortality risk in middle aged and older populations (11-13). Therefore, both inflammation and cognitive function have important implications for mortality risk throughout the aging process. It is also important to examine whether biological sex modifies this relationship, as evidence suggests that sex differences exist in the relationships between CRP, cognitive function, and mortality risk (14-16). However, there is limited evidence examining whether sex differences exist when examining the joint effect of CRP and cognitive function on mortality risk (2).

Since the likelihood of both decreased cognitive function (17) and increased inflammation (18) are more common in an older population, examining the effects of cognitive function, CRP concentration, and mortality risk in older adults remains an important research area. The primary aim of this study was to examine the joint effect of cognitive function and CRP on all-cause mortality risk in a large, nationally representative sample of United States

(U.S.) older adults. The secondary aim was to examine the sex-stratified differences in this relationship.

Methods

Study Population

This study utilized four years of data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES). The NHANES is a continuous survey conducted by the National Center for Health Statistics to estimate the prevalence of and risk factors for major diseases (19). The NHANES utilizes a complex, multistage probability sampling design to obtain a representative sample of the noninstitutionalized U.S. population. Final sample included 749 and 586 male and female participants ≥ 60 years of age, respectively. Testing and examination procedures were approved by the research and ethics review board of the National Center for Health Statistics and all participants provided informed consent (20).

Covariates

Four categories of race/ethnicity were used: non-Hispanic White, non-Hispanic Black, Mexican American, and other. Education was classified as less than high school, high school graduate, and more than high school. Glycohemoglobin (HbA1c%) was divided into three categories based on recommendations for the diagnosis of diabetes mellitus by the American Diabetes Association: <5.7%, 5.7 to 6.4%, and ≥ 6.5% (21). Non-high-density lipoprotein cholesterol (non-HDL-C), calculated by subtracting HDL-C from total cholesterol, was divided into four categories: <130, 130-160, 160-190, and ≥ 190 mg/dL (22). Reduced HDL-C was dichotomized (yes/no) for male participants (<40mg/dL, or drug treatment) and female participants (<50 mg/dL, or drug treatment) (23). Elevated waist circumference (WC) was

dichotomized (yes/no) based on the U.S Department of Health and Human Services classifications of overweight and obesity for males (≥102 cm) and females (≥88cm) (24). Blood pressure was categorized based on the 2017 American College of Cardiology and American Heart Association guidelines (25). Total physical activity volume (TPAV) was determined based on weekly MET values of aerobic PA across three PA domains (26).

Cognitive Function and CRP

Cognitive function was assessed using the Digit Symbol Substitution Test (DSST). The DSST requires participants to copy symbols that are paired with numbers during a period of two minutes. Participants are then scored by the number of correct symbols drawn within the time limit. The DSST is a component of the Wechsler Adult Intelligence Test that requires response speed, sustained attention, visual spatial skills, associative learning, and memory (27). Based on the median DSST score (DSST value of 51), cognitive function was dichotomized as high cognitive function (> 51 correct) or low cognitive function (≤ 51 correct) (12).

High-sensitivity CRP assays were performed on a Behring Nephelometer (Dade Behring Diagnostics, Somerville, NJ) for quantitative CRP determination (28). CRP was dichotomized as low to average CRP concentration (≤ 3 mg/L) and elevated CRP concentration (>3-10 mg/L). The CRP ranges were based on risk stratification determined by the Center for Disease Control and Prevention and the American Heart Association identifying both low risk and high-risk CRP cut points (29). A four-level combined cognitive function and CRP variable was created: high cognitive function and low to average CRP; high cognitive function and high CRP; low cognitive function and low to average CRP; and low cognitive function and high CRP.

Mortality

The National Center for Health Statistics linked death records from the National Death Index to the 1999-2002 NHANES participants using a process outlined elsewhere (30). Cause of death was determined and classified using the International Statistical Classification of Diseases, Injuries, and Causes of Death-10 codes for participants who were identified as deceased. All-cause mortality was the primary dependent variable examined in this study.

Statistical Analysis

The data in this study were managed using SAS (Version 9.4; SAS Institute, Inc., Cary, NC). SAS was used to conduct complex variable recodes, data coding validation, and to conduct the analysis incorporating sampling weights within the context of the correlated multi-stage complex design inherent to the NHANES. PROC SURVEYMEANS was used to produce mean, median, quartiles, and 95% confidence intervals for covariates. Statistical significance was assessed through the 95% confidence intervals produced using PROC SURVEYMEANS and non-overlapping confidence intervals indicated statistical significance at $P < 0.05$. Weighted prevalence estimates were produced using PROC SURVEYFREQ and Cox proportional hazard ratios were produced using PROC SURVEYPHREG. Kaplan-Meier survival curves were produced with PROC LIFETEST. Any participants who responded, “don’t know/not sure”, refused to answer, or had missing responses for any of the questions or measures were excluded from the final analysis. A forward selection process based on the results of the Cox proportional hazards regression analysis was used to generate three models for analysis. These included a crude Model 1, Model 2 adjusted for demographics including education, age, and race/ethnicity, and Model 3 adjusted for all Model 2 covariates and CVD-related risk factors (i.e., smoking status, non-HDL-C, HDL-C, HbA1c%, blood pressure, WC, and TPAV).

Results

Table 1. Study Characteristics of Men ≥ 60 Years of Age: NHANES 1999-2002 ($N = 749$).

	Point Estimate (95% CI*)			
Variable	High CRP and Low Cognitive Function	High CRP and High Cognitive Function	Low to Average CRP and Low Cognitive Function	Low to Average CRP and High Cognitive Function
N, % of total sample	151 (20.2)	101 (13.5)	264 (35.2)	233 (31.1)
DSST, median number correct	34.0 (31.2-36.7)	56.8 (54.2-59.4)	35.3 (33.6-37.0)	59.6 (58.0-61.2)
Race/ethnicity				
%, nH-White	49.7	81.2	56.1	78.1
%, nH-Black	17.9	9.9	14.8	5.6
%, Mexican American	29.8	8.9	23.5	11.6
%, Other	2.6	0.0	5.6	4.7
Total Weekly Physical Activity Volume, median, MET/min/wk^{-1}	751.6 (513.6-989.5)	566.2 (300.1-832.4)	564.4 (388.9-739.8)	634.2 (511.4-757.0)
Elevated serum cotinine concentration**, %	25.2	19.8	17.8	11.2
WC, median, cm	105.0 (101.9-108.1)	105.5 (103.0-108.0)	102.2 (100.3-104.1)	101.5 (99.4-103.5)
Non-HDL-C, median, mg/dl	157.1 (147.8-166.5)	157.1 (151.2-163.1)	145.4 (140.2-150.7)	151.1 (144.6-157.6)
HDL-C, median, mg/dl	41.8 (39.4-44.1)	41.7 (39.5-43.8)	43.3 (40.7-45.8)	45.4 (42.8-45.8)
HbA1c, median %	5.60 (5.47-5.74)	5.54 (5.45-5.63)	5.49 (5.43-5.55)	5.39 (5.33-5.45)
Mortality, % died	63.6	41.6	60.2	33.9

*Non-overlapping confidence intervals indicate statistical significance at $P < 0.05$.

**Elevated serum cotinine concentration: serum cotinine ≥ 3 ng/ml.

Table 2. Study Characteristics of Women ≥ 60 Years of Age: NHANES 1999-2002 ($N = 586$).

Variable	High CRP and Low Cognitive Function	High CRP and High Cognitive Function	Low to Average CRP and Low Cognitive Function	Low to Average CRP and High Cognitive Function
N, % of total sample	115 (19.6)	141 (24.1)	142 (24.2)	188 (32.1)
DSST, median number correct	34.4 (31.4-37.3)	59.9 (56.5-63.3)	34.3 (31.5-37.2)	58.2 (56.2-60.1)
Race/ethnicity				
%, nH-White	33.9	76.6	51.4	81.9
%, nH-Black	16.5	8.5	17.6	5.3
%, Mexican American	37.4	13.5	20.4	8.5
%, Other	12.2	1.4	10.6	4.3
Total Weekly Physical Activity Volume, median, MET/min/wk^{-1}	250.0 (151.4-348.6)	521.3 (320.8-721.8)	587.8 (399.6-776.0)	496.3 (363.7-628.8)
Elevated serum cotinine concentration**, %	9.6	9.2	14.8	11.7
WC, median, cm	96.3 (93.2-99.4)	97.8 (94.0-101.6)	92.3 (89.6-95.0)	90.8 (88.2-93.4)
Non-HDL-C, median, mg/dl	171.0 (162.7-179.4)	162.1 (155.1-169.2)	153.4 (139.4-167.4)	157.4 (151.5-163.2)
HDL-C, median, mg/dl	53.3 (48.5-58.1)	57.0 (53.6-60.4)	56.5 (52.0-61.0)	59.3 (55.6-62.9)
HbA1c, median %	5.54 (5.39-5.69)	5.37 (5.30-5.44)	5.43 (5.35-5.51)	5.35 (5.29-5.40)
Mortality, % died	43.5	29.8	50.0	30.3

*Non-overlapping confidence intervals indicate statistical significance at $P < 0.05$.

**Elevated serum cotinine concentration: serum cotinine ≥ 3 ng/ml.

The study characteristics of the male and female participants according to CRP concentration and cognitive function are summarized in Tables 1 and 2, respectively. Table 3 illustrates the results of the Cox proportional hazards regression analysis examining the association between cognitive function, CRP concentration, and all-cause mortality risk. Crude analysis revealed an approximate 3-fold ($P < 0.0001$) increase in all-cause mortality risk in participants with low cognitive function and high CRP when compared to a referent group with high cognitive function and low to average CRP. Following adjustment for demographic factors, the risk of all-cause mortality was slightly attenuated but remained statistically significant in participants with low cognitive function and low to average CRP and with low cognitive function and high CRP ($P < 0.0001$ for both). A significant increase in all-cause mortality risk was maintained in participants with low cognitive function, regardless of CRP concentration ($P < 0.0001$ for both) following full adjustment.

Table 3. Combined Effect of Cognitive Function and CRP on All-Cause Mortality Risk in U.S. Adults ≥ 60 Years of Age: NHANES 1999-2002.

Variable	Model 1 HR[a] (95% CI)	Model 2 HR[b] (95% CI)	Model 3 HR[c] (95% CI)
High Cognitive Function and Low to Average CRP	1.00	1.00	1.00
High Cognitive Function and High CRP	1.17 (0.87-1.56)	1.09 (0.81-1.47)	1.10 (0.83-1.47)
Low Cognitive Function and Low to Average CRP	2.50 (1.97-3.17)*	1.92 (1.51-2.43)*	1.78 (1.38-2.29)*
Low Cognitive Function and High CRP	2.63 (2.01-3.44)*	2.30 (1.78-2.99)*	2.37 (1.82-3.09)*

[a] Unadjusted crude model. [b] Adjusted for education, age, and race/ethnicity. [c] Adjusted for education, age, race/ethnicity, smoking status, non-HDL-C, HDL-C, HbA1c%, blood pressure, WC, and TPAV.

*$P < 0.0001$.

Table 4 illustrates the results of the Cox proportional hazards regression analysis stratified by sex. Crude analysis revealed a 3-fold ($P < 0.0001$ for both) increase in all-cause mortality risk in male participants with low cognitive function and low to average CRP and in male participants with low cognitive function and high CRP. After adjusting for demographic factors, all-cause mortality risk was slightly attenuated but remained significant in male participants with low cognitive function and low to average CRP and in male participants with low cognitive function and high CRP ($P < 0.0001$ for both). Significance was maintained in those with low cognitive function after adjusting for CVD-related risk factors, regardless of CRP concentration.

In female participants, crude analysis revealed an approximate 2-fold increase in all-cause mortality risk in participants with low cognitive function and low to average CRP and in participants with low cognitive function and high CRP. After adjusting for demographic factors, all-cause mortality risk was attenuated but remained significant in female participants with low cognitive function and low to average CRP ($P < 0.01$) and in female participants with low cognitive function and high CRP ($P < 0.05$). After adjusting for CVD-related risk factors, a significant increase in all-cause mortality risk only remained in female participants with low cognitive function and low to average CRP ($P < 0.05$). A significant increase in all-cause mortality risk was not observed in female participants with low cognitive function and high CRP following adjustment for CVD-related risk factors.

Table 4. Combined Effect of Cognitive Function and CRP on All-Cause Mortality Risk according to Sex in U.S. Adults ≥ 60 Years of Age: NHANES 1999-2002.

	Variable	Model 1	Model 2	Model 3
Men	High Cognitive Function and Low to Average CRP	1.00	1.00	1.00
	High Cognitive Function and High CRP	1.47 (0.93-2.34)	1.33 (0.81-2.20)	1.26 (0.74-2.13)
	Low Cognitive Function and Low to Average CRP	2.69 (1.94-3.74)*	1.73 (1.18-2.54) **	1.67 (1.10-2.54)***
	Low Cognitive Function and High CRP	3.34 (2.32-4.81)*	2.67 (1.81-3.94) *	2.74 (1.82-4.12)*
Women	High Cognitive Function and Low to Average CRP	1.00	1.00	1.00
	High Cognitive Function and High CRP	1.00 (0.63-1.58)	0.97 (0.60-1.57)	0.96 (0.61-1.53)
	Low Cognitive Function and Low to Average CRP	2.24 (1.57-3.18)*	1.90 (1.29-2.80)**	1.71 (1.14-2.59)***
	Low Cognitive Function and High CRP	1.99 (1.17-3.41)***	1.89 (1.02-3.50)***	1.75 (0.90-3.43)

[a] Unadjusted crude model. [b] Adjusted for sex, education, age, and race/ethnicity. [c] Adjusted for age, sex, education, race/ethnicity, smoking status, non-HDL-C, HDL-C, HbA1c%, blood pressure, WC, and TPAV.

* $P < 0.0001$

** $P < 0.01$

***P < 0.05

Figure 1 illustrates the Kaplan-Meier survival curves for male participants stratified by the cognitive function-CRP variable. A significant difference in mortality was observed (log-rank test, $P < 0.0001$) between male participants with high cognitive function and male participants with low cognitive function. Figure 2 illustrates the Kaplan-Meier survival curves for female participants, indicating a significant difference (log-rank test, $P = 0.0001$) in mortality among the four groups, with the greatest mortality observed in female participants with low cognitive function and low to average CRP.

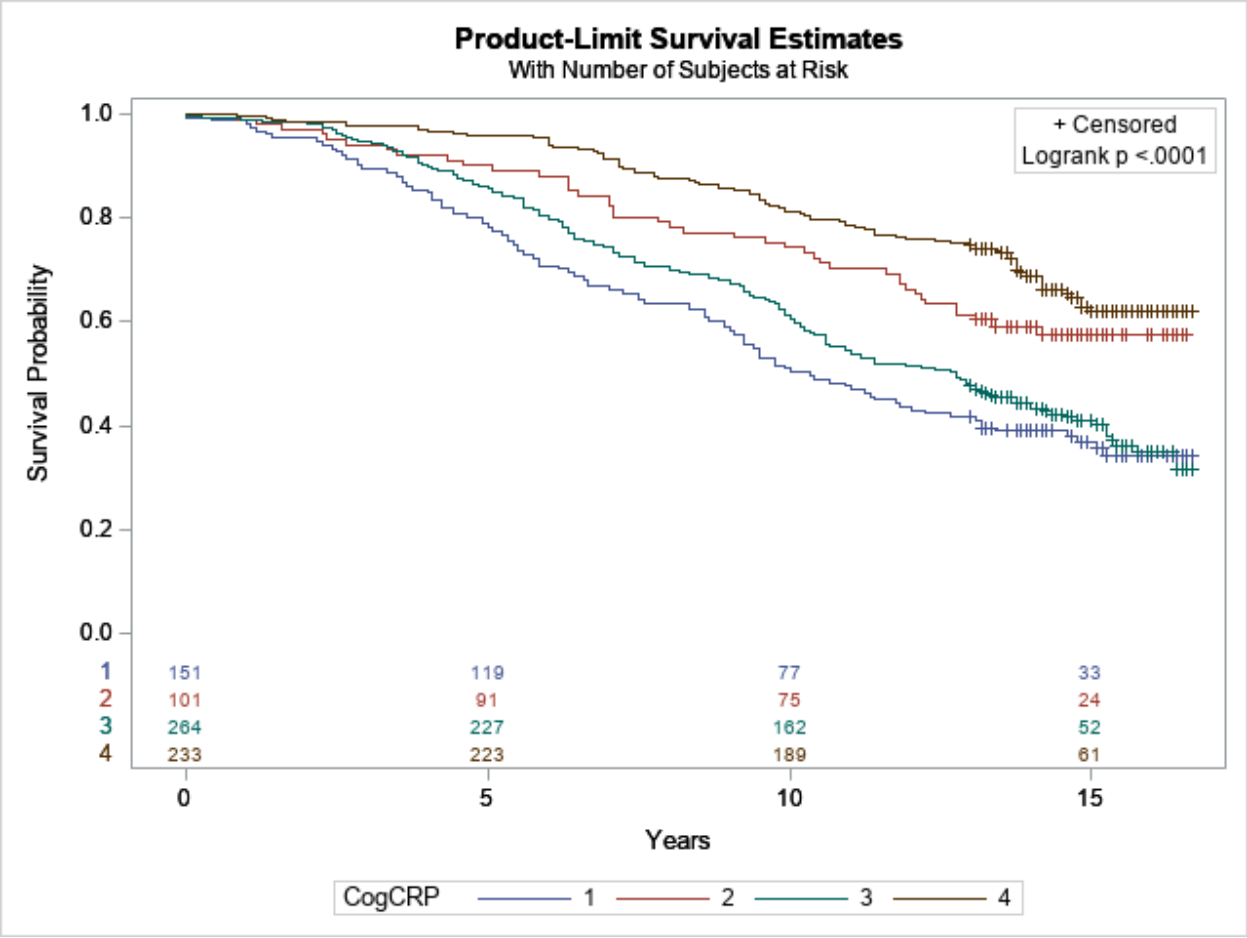

Figure 1. Kaplan-Meier survival curves for U.S. older adult male participants stratified by the four-level joint cognitive function-CRP variable. Cognitive Function-CRP 1 (low cognitive function and high CRP), Cognitive Function-CRP 2 (high cognitive function and high CRP), Cognitive Function-CRP 3 (low cognitive function and low to average CRP), Cognitive Function-CRP 4 (high cognitive function and low to average CRP).

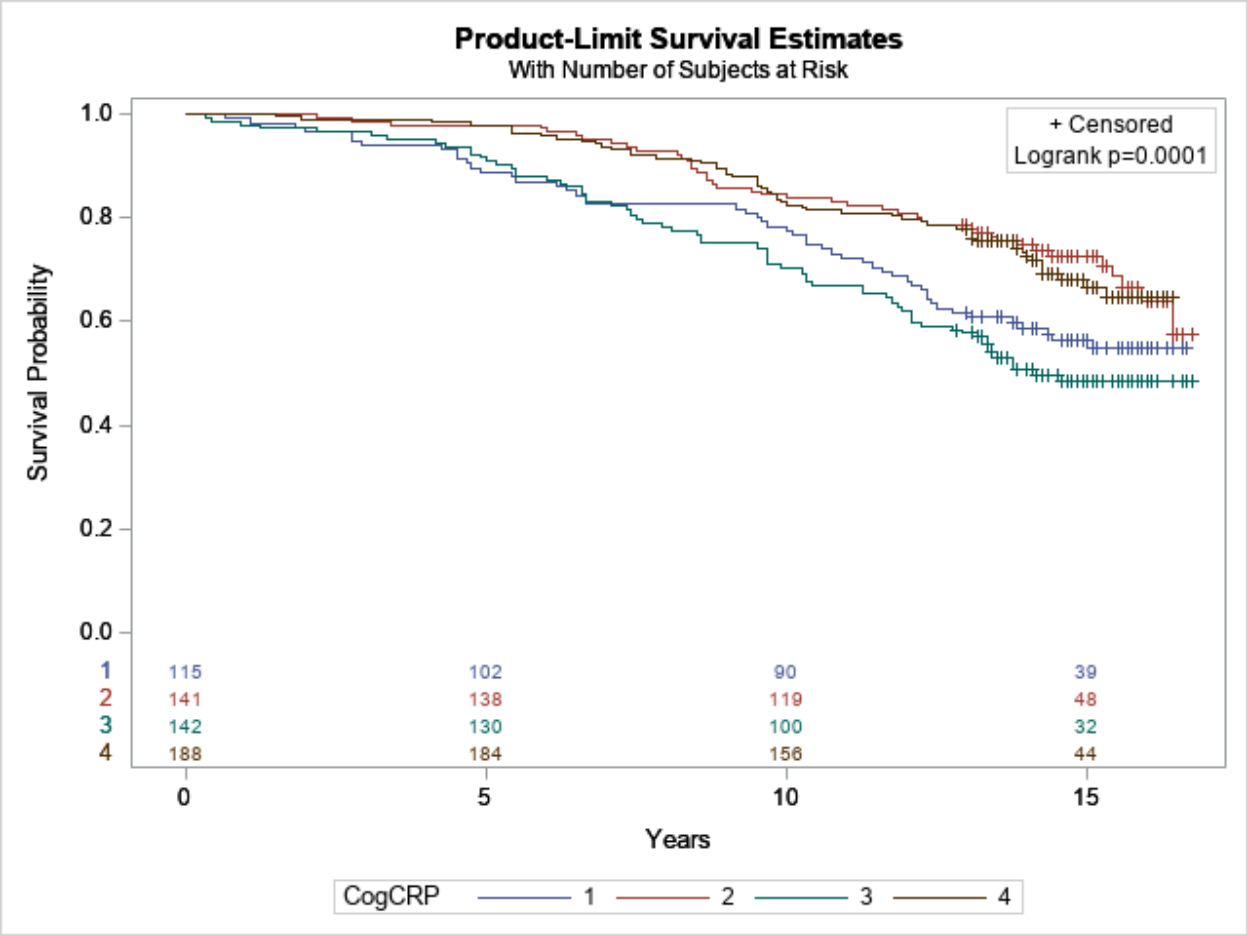

Figure 2. Kaplan-Meier survival curves for U.S. older adult female participants stratified by the four-level joint cognitive function-CRP variable. Cognitive Function-CRP 1 (low cognitive function and high CRP), Cognitive Function-CRP 2 (high cognitive function and high CRP), Cognitive Function-CRP 3 (low cognitive function and low to average CRP), Cognitive Function-CRP 4 (high cognitive function and low to average CRP).

Discussion:

Our findings suggest that low cognitive function is associated with a statistically significant increase in all-cause mortality risk independent of CRP concentration. Sex-stratified analyses revealed a significant increase in all-cause mortality risk in male participants with low cognitive function, regardless of CRP concentration. However, a significant increase in all-cause mortality risk in female participants was only observed in those with low cognitive function and low to average CRP following full adjustment. Our findings add to the limited evidence

suggesting low cognitive function is an independent predictor of increased all-cause mortality risk in older adults, independent of CRP concentration. These findings also add to the paucity of evidence suggesting sex differences may exist when examining the joint effect of CRP and cognitive function on mortality risk (2).

Our findings are similar to those reported in a 2019 prospective cohort study conducted by Chen et al. which found an increased mortality risk in older adults with low cognitive function, regardless of CRP concentration. These investigators examined the joint effect of CRP concentration and cognitive performance on all-cause mortality risk in adults (≥ 80 years of age) in the Chinese Longitudinal Healthy Longevity Survey using a four-level joint CRP and cognition variable (i.e., cognitive function was dichotomized as cognitive impairment and normal cognition based on results of the Mini-Mental Status Examination (MMSE)). These investigators reported a 2.4-fold and a 3.6-fold increase in all-cause mortality risk in participants with CRP concentrations ≤ 3.0 mg/L and cognitive impairment and in participants with a CRP concentration > 3.0 mg/L and cognitive impairment, respectively. These results are similar to those reported in the present study as no significant differences in all-cause mortality risk were observed based on CRP concentration in those with low cognitive function.

These investigators also reported that participants with a CRP concentration > 3 mg/L and normal cognition had a 70% increase in all-cause mortality risk, compared to a referent group with CRP concentration ≤ 3.0 mg/L and normal cognition. These results contrast with those of the present study, as a significant increase in all-cause mortality risk was not revealed in participants with high cognitive function and high CRP (CRP > 3 mg/L). This may be due to differences in the populations analyzed and the measures of cognitive function utilized. The population examined by Chen et al. (2019) included Chinese oldest-old adults (≥ 80 years of

age). Our study examined older adult (≥ 60 years of age) NHANES participants. Additionally, Chen et al. (2019) assessed cognitive function using the MMSE; cognitive function was assessed using the DSST in the present study. The MMSE is an index of global cognitive function; while the DSST assesses components of executive function (27, 31). This is noteworthy because some evidence suggests that executive function may be a stronger predictor of mortality when compared to global cognitive function (32, 33).

The results of the present study also expand upon previous literature examining the joint effects of CVD risk and cognitive function on all-cause mortality risk. In 2017, Loprinzi et al. similarly examined the joint effects of CVD risk factors, using a variable that included CRP concentration, and DSST-assessed cognitive function on all-cause mortality risk among older adult (≥ 60 years of age) participants in the 1999-2002 NHANES (12). These investigators reported that low cognitive function (DSST score < 42) was associated with a two-fold increase in all-cause mortality risk, independent of CVD risk. Our study expands on this finding, illustrating that low cognitive function is associated with augmented all-cause mortality risk, independent of CRP as an isolated CVD risk factor. Therefore, although an aggregate of risk factors may lead to compounding effects on mortality risk, it remains important to examine isolated CVD risk factors.

The associations between cognitive function, CRP, and mortality risk may also be modified by sex. Doran et al. (2013) examined the relationship between increased CRP and mortality risk using sex-stratified analyses (15). These investigators reported that males with CRP concentrations > 3.0 mg/L had a 57% increase in all-cause mortality risk compared to those with a CRP ≤ 3.0 mg/L. A similar statistically significant increase in all-cause mortality risk was not observed in females. In 2015, Perna et al. examined the association between cognitive

impairment and all-cause and cause-specific mortality (16). Cognitive impairment was assessed by the Cognitive Telephone Screening Instrument (COGTEL), with higher scores indicating greater cognitive function. No significant increases in all-cause mortality risk were observed in females with low COGTEL scores, however, a 90% increase in all-cause mortality risk was observed in males with low COGTEL scores. Although these studies examined CRP concentration and cognitive function as independent predictors of mortality risk, these results suggest that sex differences in the associations between CRP concentration, cognitive function, and mortality risk exist. The results of the present study expand on these findings, suggesting that sex differences also exist concerning the joint effect of cognitive function and CRP concentration on mortality risk.

When examining the combined associations of CRP concentration and cognitive function according to sex, Chen et al. (2019) reported that mortality risk was stronger in males (2). Among those with a CRP concentration > 3 mg/L and cognitive impairment, females had an approximate 3-fold increase in all-cause mortality risk, while males had a 4.3-fold increase in all-cause mortality risk. These findings were similar to those presented, as the combined effect of CRP and cognitive function on all-cause mortality risk was also stronger in males. However, in contrast to the findings of Chen et al. (2019), our fully-adjusted analyses suggests that female participants with high CRP concentration and low cognitive function do not possess statistically significantly increased all-cause mortality risk. This may have occurred due to gender differences in baseline CRP concentration. Higher baseline CRP values have been observed in women when compared to men (15, 34). Additionally, an elevation from one's baseline, rather than an absolute value, may be an important consideration when examining the association between CRP concentration and mortality risk in women (15).

The findings of this study are important because it suggests that maintaining cognitive function may be an important consideration for improved longevity. The findings also suggest that DSST-assessed cognitive function may be a powerful prognostic tool when assessing mortality risk in older adults. Our study adds to the limited evidence examining sex differences in the joint association between cognitive function and CRP concentration on all-cause mortality risk. Our findings revealed that males with low cognitive function have a greater risk of all-cause mortality, independent of CRP concentration. However, in females, a significant increase in risk was only observed in those with low cognitive function and low to average CRP concentration. These findings suggest that sex differences may exist when examining the joint effect of cognitive function and CRP concentration on all-cause mortality risk.

The strengths of our study include the contribution our findings make to the limited evidence examining the joint effect of cognitive function and CRP concentration on all-cause mortality risk and the sex differences in this relationship. Second, the NHANES includes a large, population-based, nationally representative sample which allows results to be generalized to the older U.S. adult population. Lastly, cognitive function was objectively measured, minimizing the effects of recall and reporting biases. The present study also includes some inherent limitations. The potential changes in cognitive function between initial measurement and death are not assessed. Additionally, cause-specific mortality was not assessed in the present study. The effect of low cognitive function on all-cause mortality risk may differ for CVD or diabetes-related mortality and requires further examination.

Conclusion

Our results revealed that in a large, nationally representative sample of older U.S. adults, low cognitive function was associated with a statistically significant increase in all-cause

mortality risk, independent of CRP concentration. Our results also indicate that sex differences may exist when examining the joint effects of cognitive function and CRP concentration on all-cause mortality risk.

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Vita

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