Title
Cognitive Function and Physical Function in Persons with Rheumatoid Arthritis

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Publication Date
2012

Peer reviewed|Thesis/dissertation

Cognitive Function and Physical Function in Persons with Rheumatoid Arthritis

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Acknowledgements

I am delighted to acknowledge special individuals and organizations that were critical in the completion of my dissertation. To all of you, I dedicate this beginning to my program of research at the University of California, San Francisco.

I am deeply thankful to the members of my dissertation committee for sharing their expertise and guidance. Patricia Katz graciously shared her data and provided me all the opportunities that I would not have had without her. Her expertise in the area of functioning and arthritis care was critical for conducting my dissertation study. Laura Julian's neuropsychological perspective and thoughtful guidance were invaluable. I am thankful for Margaret Wallhagen, my dissertation chair, mentor, and advisor, who has been a constant source of support and encouragement. I am deeply grateful for her expertise in guiding my dissertation study and my nursing career. I am also thankful to Kenneth Covinsky for his professional advice on geriatric care and research methods in the early phase of the dissertation.

I am sincerely thankful to Heather Leutwyler for providing me the valuable opportunity to learn how to conduct a research study and collaborate with personnel from diverse disciplines. I thank Erin Hubbard for being a kind and supportive colleague. I thank Steve Paul for his expert advice on statistics and data analysis. I appreciate Robert Slaughter, Jyu-Lin Chen, Bruce Cooper, Abbey Alkon, and Lisa Thompson for providing me the exceptional experience of teaching and communicating with students.

I am grateful to all the patients who have opened my eyes to the issue of poor functional status among older adults with chronic diseases. I thank the UCSF/John A. Hartford Center of Geriatric Nursing Excellence for creating the opportunity to

collaborate with gerontological experts and for providing me the generous support needed to complete my nursing doctoral program.

I thank my doctoral nursing student colleagues, Sunjoo Boo, Yoonmee Joo, and Heeok Park, for believing in me and encouraging me. I give special thanks to my friends, Bomin Shim, Eunjung Kim, Hyejung Shin, and Dorothy Ahn for their constant support and companionship.

I thank my family members, maternal grandparents, aunt Youngiee, uncle Hyunchul, Jina Hwang, and Hyein Kim, for their trust and encouragement. I am thankful to my sister, Yoonjung, for her ongoing support and love. She was the one who could make me feel all kinds of emotions including joy and happiness.

I give my mother my heartfelt gratitude for listening to my daily struggles and successes involved with my doctoral study and for encouraging me to find my strength, confidence, and passion. I deeply thank my father, the man that I admire and love the most, for his constant support and devoted affection during the long days of my nursing education.

Last, but certainly not least, I share this glorious moment to my grandmother in heaven for watching over me and helping me to complete my studies.

Abstract

The purpose of this dissertation was to examine the prevalence and possible predictors of cognitive impairment, and the relationship of cognitive impairment with functional limitations and disability in persons with rheumatoid arthritis (RA). Individuals from a longitudinal cohort study of RA participated in study visits that included physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices covering a range of cognitive domains. On each test, subjects were classified as impaired if they performed 1 SD below age-based population norms. Total cognitive function scores were calculated by summing the transformed scores (range 0-16; higher scores=greater impairment). Functional limitations and disability were assessed with both performance-based and self-reported measures. Logistic regression analyses were conducted to identify which of the following were significant predictors of cognitive impairment: gender, race, income, education, depression, disease duration, disease severity, C-reactive protein (CRP), glucocorticoid use, and cardiovascular disease (CVD) risk factors. Multiple regression analyses, controlling for gender, race, education, marital status, income, disease duration, disease severity, CRP, and depression were conducted to identify whether cognitive impairment was independently associated with physical function difficulties. The proportion of persons who were classified as cognitively impaired on at least 4 of 16 indices was 31%. Education, income, glucocorticoid use, and CVD risk factors independently predicted cognitive impairment controlling for gender, race, disease duration, disease severity, CRP, and depression. Individuals with cognitive impairment were more likely to have low education (OR = 6.18, 95% CI: 1.6-23.87), low income

(OR = 7.12, 95% CI: 1.35-37.51), use oral glucocorticoids (OR = 2.92, 95% CI: 1.05-8.12), and have increased CVD risk factors (OR = 1.61, 95% CI: 1.19-2.17 per risk factor). In multivariate regression models, total cognitive function scores were significantly associated with greater functional limitations ($p<.05$) but not with disability ($p=.120$). The findings of this study suggest that the burden of cognitive impairment in RA is significant, and future studies identifying specific etiological contributors to cognitive impairment are warranted. In addition, consideration of cognitive impairment may be warranted to improve functional status in persons with RA.

Table of Contents

Copyright …….…… ii

Acknowledgements ……..……...…… iii

Abstract ……..……....… v

Table of Contents ……..……..……. vii

Chapter 1 ……..…… 1

Introduction

Chapter 2 ……..……... 15

Literature Review

Paper 1: The Relationship between Cognitive Function and Physical Function in Older Adults with Rheumatoid Arthritis: A Literature Review

Chapter 3 ……..…….…. 52

Theoretical Framework

Paper 2: Disability Intervention Model for Older Adults with Arthritis: Incorporating the Disablement Process Model and the Theory of Symptom Management

Chapter 4 ……..……..……. 77

Paper 3: Cognitive Impairment in Persons with Rheumatoid Arthritis

Chapter 5 ……..……. 101

Paper 4: The Relationship between Cognitive Function and Physical Function in Persons with Rheumatoid Arthritis

Chapter 6 ……..……...…….……...….…… 125

Synthesis

Publishing Agreement ……..…… 147

Chapter 1: Introduction

My overarching research interest, improving physical function in older adults with chronic disease, especially arthritis, evolved from my clinical experiences. After completing my undergraduate nursing program, I worked as a registered nurse in a medical unit in the Asan Medical Center in Seoul, Korea. I took care of patients who had not only life-threatening cardiac problems, but also systemic inflammatory diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). They were suffering not only from physical health problems including chronic pain and disability, but also from psychological distress and cognitive impairment. In addition, many older patients, no matter what the main reason was for them to seek health care, had multiple chronic health problems. However, many of these older patients had neglected their symptoms and refused formal health care because they thought that these disabling symptoms were just a part of the normal aging process. They endured their symptoms using only over-the-counter medications or complementary therapies by themselves for long periods. Most patients had little knowledge about their medical conditions, the treatments being offered or what might be available to them, and ongoing self-management strategies. This lack of knowledge exacerbated their health problems even more.

Because arthritis is an incurable chronic disease, one of the most important interventions is educating patients about how to self-manage and cope with their symptoms. Considering the characteristics of older adults, cognitive function is an apparently important factor for maximizing the effect of educational interventions. As a researcher, if I could identify the role of cognitive function as a significant factor that might affect physical function difficulties, this information would be helpful for

designing effective and targeted interventions to improve physical function in older adults with arthritis. This is why I wanted to explore the relationship between cognitive function and physical function in this population. I hope that through my doctoral research program, I may find avenues to improve physical function in older adults with arthritis and continue to advance nursing as a science and a profession.

RA is a systemic inflammatory autoimmune disease that is characterized by pain, joint stiffness, joint swelling, fatigue, and subsequent functional limitations and disability (Taibi & Bourguignon, 2003). RA affects 1-2 million individuals in the United States and is two to three times more common in women than men (Abdel-Nasser, Rasker, & Vaikenburg, 1997; Mikuls, 2010). Approximately 25-50% of persons with RA lose the ability to work within 10-20 years of diagnosis, and their mortality risks are 60-70% higher than those of the general population (Mikuls, 2010). The proportion of persons living with RA has increased over time due to longevity and disease chronicity (Hootman & Helmick, 2006). Therefore, RA-related adverse outcomes for functional status, health care costs, morbidity or mortality, and psychological well-being are inclined to increase in these patients (Helmick et al., 2008). Understanding the risk factors that aggravate functional limitations and disability is important for developing effective intervention strategies to prevent functional decline, maintain functional independence, and improve quality of life (Dunlop, et al., 2005).

The primary purpose of this dissertation was to explore the relationship between cognitive function and physical function in persons with RA. The hypothesis was that cognitive impairment would be independently related to higher levels of physical function difficulties (functional limitations and disability) in persons with RA after

controlling for other sociodemographic and disease-related variables. The secondary purpose of this dissertation was to examine the prevalence and potential predictors of cognitive impairment in persons with RA. The hypothesis was that disease-related factors would be significant factors affecting cognitive impairment in persons with RA after controlling for other sociodemographic variables.

Backgrounds and Significance

Cognitive function is an important feature in maintaining function, health, and quality of life in older adults (Appenzeller, Bertolo, & Costallat, 2004). Persons with impaired cognitive function have decreased functional independence, reduced well-being, and increased mortality risk (Bennett et al., 2002; Neale, Brayne, & Johnson, 2001). Cognitive impairment and disability are relatively common problems among older adults that make them unable to live independently (Buchner, Beresford, Larson, LaCroix, & Wagner, 1992; Hebert, Brayne, & Spiegelhalter, 1999; Larson, Kukull, & Katzman, 1992). For persons with chronic diseases such as RA, intact cognitive function is crucial for performing daily activities and maintaining disease management skills, including adhering to medication regimens, planning and initiating activities based on one's current condition, changing plans if pain unexpectedly worsens, and inhibiting behaviors which aggravate pain or health status (Abeare et al., 2010).

Cognitive function has not been extensively studied in persons with RA even though several mechanisms may influence cognitive function in these patients, including the systemic inflammatory process, chronic pain, fatigue, psychological distress, and continuous corticosteroid use (Appenzeller, et al., 2004). To date, only two studies have evaluated cognitive dysfunction in well characterized cohorts of RA patients using a

comprehensive neuropsychological test battery that extends beyond general mental status screening exams, such as the Mini-Mental State Examination (MMSE). In one study, cognitive dysfunction was observed to be common in RA patients with prevalence rates ranging from 38% in domains evaluating divided/sustained attention and mental flexibility to 71% in domains evaluating visuo-spatial and planning functions (Bartolini et al., 2002). In this cohort, cognitive dysfunction was also associated with neuroimaging findings, including hypoperfusion on brain single photon emission computed tomography (SPECT) and increased white matter alterations on magnetic resonance imaging (MRI). Additionally, Appenzeller and colleagues (2004) found cognitive impairment in 30% of the RA cohort as compared to 8% of age and sex matched healthy controls. RA patients had significantly worse outcomes in verbal fluency and episodic memory. These few studies have important implications in that they highlight the potential burden of cognitive impairment and its possible risk factors in RA patients who have not been widely investigated.

The relationship between global cognitive function and daily functional status has been well-studied in the general population (Reed, Jagust, & Seab, 1989; Skurla, Rogers, & Sunderland, 1988). Among the various domains of cognitive function in older adults, executive function and memory have consistently been found to be associated with everyday function, including activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (Cahn-Weiner, Boyle, & Malloy, 2002; Cahn-Weiner et al., 2007; Farias, Mungas, Reed, Haan, & Jagust, 2004; Tomaszewski Farias et al., 2009). People with more impairment in executive function and memory had more functional limitations (Cahn-Weiner, et al., 2007). Additionally, declines in executive function and

memory studied over time independently contributed to declines in daily function in older adults (Tomaszewski Farias, et al., 2009).

A number of studies have assessed cognitive function as one of various risk factors or predictors that might exacerbate functional limitations or disability in a large sample of community-dwelling older adults with a wide range of chronic health conditions, including arthritis (Auyeung et al., 2008; Dunlop, et al., 2005; Greiner, Snowdon, & Schmitt, 1996; Raji et al., 2005; Wang, van Belle, Kukull, & Larson, 2002). However, several limitations are present. First, the use of diverse terms and concepts regarding cognitive function and physical function hindered researching and comparing studies. Most researchers did not specifically define the main concepts of cognitive function and physical function used in their studies. A number of terms, including cognition, cognitive function, cognitive status, neuropsychological status, general mental status, and executive function were used to represent the concept of cognitive function. The heterogeneity of criteria for classifying cognitive impairment also precluded study comparisons. Many studies followed the definitions of functional limitations and disability in the Disablement Process Model proposed by Verbrugge and Jette (1994). However, most of the studies used both concepts interchangeably to represent the notion of physical function, and assessed them as functional outcomes.

Second, as there is no standardized test for examining cognitive function, a wide range of measures was used for cognitive function assessment. Most studies used only one instrument, mostly the MMSE, to assess global cognitive function. A paucity of studies used a range of neuropsychological tests in addition to the measurement of global mental status (Atkinson et al., 2007; Eggermont, Milberg, Lipsitz, Scherder, & Leveille,

2009; Rosano et al., 2005). Even among studies which examined the same specific subdomain (i.e., executive function) of cognitive function, different types of neuropsychological tests were used, confusing the interpretation of the findings and making comparisons across studies difficult.

Third, many studies used either self-reported information or performance-based tests in assessing physical function, while few studies used both. Some studies (Auyeung, et al., 2008; Kuo, Leveille, Yu, & Milberg, 2007; Samper Ternent, Al Snih, Raji, Markides, & Ottenbacher, 2008; Wang, et al., 2002) found that cognitive function was related to both self-reported disability and performance-based tests. However, two studies (Fitzpatrick, et al., 2007; Weiner, Rudy, Morrow, Slaboda, & Lieber, 2006) found that cognitive function was significantly correlated with performance-based physical function tests, but not with self-reported measures of disability. Therefore, using both subjective and objective measures of physical function may provide more reliable and comprehensive information in older adults who have a higher likelihood of being cognitively and physically impaired.

Fourth, no study examined the relationship between cognitive function and physical function in older adults with RA. Most population-based studies conducted secondary analyses using a large population-based sample of older adults with various chronic health conditions, including arthritis. One study by Appenzeller and colleagues (2004) specifically assessed RA patients compared to healthy controls. However, the primary purpose of this study was not to examine the relationship between cognitive function and physical function. Rather, the researchers found the lack of association indirectly in the process of investigating risk factors for incident cognitive impairment in

RA patients. In addition, this study has several aforementioned limitations to be generalized.

Older adults with RA may have an increased burden of functional limitations and disability in daily activities due to the impact of both age-related cognitive function decline and RA-related impairment. The role of cognitive function in the development of physical function difficulties has not been previously studied in this population. Therefore, this dissertation may provide a scientific foundation for future research as well as data to support designing interventions to prevent further disability, maintain functional independence, and improve quality of life.

Overview of Papers

The dissertation is organized into four parts. The first paper is a literature review of the relationship between cognitive function and physical function in older adults with or without chronic health conditions including RA. Because there was no study which specifically assessed older adults with RA, this paper included twenty seven population-based studies which examined community-dwelling, non-institutionalized older adults with several comorbid health conditions in addition to arthritis but without neurologic disorders. The major findings, limitations, and strengths of the reviewed articles were presented followed by the implications for future research and nursing practice.

The second paper presents the theoretical framework used as guidance for my research. The Disablement Process Model (Verbrugge & Jette, 1994) and the Theory of Symptom Management (Humphreys, et al., 2008) were intensively reviewed. With a comprehensive understanding of the concepts, applications, strengths, and limitations of the two models, my study model, a Disability Intervention Model for Older Adults with

Arthritis (DIMOA) has been created. The DIMOA is essentially based on the Theory of Symptom Management, with an effort to incorporate the disablement process of RA into it, so that it can be utilized as a theoretical foundation specifically for RA management in research and clinical practice.

The third paper presents the prevalence and potential predictors of cognitive impairment in individuals from a longitudinal cohort study of RA. About one-third of RA patients were cognitively impaired. Persons with less education, less income, steroid use, and more cardiovascular disease risk factors were more likely to have cognitive impairment in this cohort. These findings suggest that the burden of cognitive impairment in RA is significant, and there is a need to identify specific etiological contributors to cognitive impairment in this population.

The final paper reports the relationship between cognitive impairment and physical function difficulties in the same sample noted above. Cognitive impairment was significantly associated with greater self-reported and performance-based functional limitations but not with greater disability. The findings of this study suggest that consideration of cognitive impairment may be warranted to improve functional status in persons with RA. The final paper is followed by a synthesis of findings, implications for clinical practice and suggestions for future research.

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Chapter 2: Literature Review

Paper 1: The Relationship between Cognitive Function and Physical Function in Older Adults with Rheumatoid Arthritis: A Literature Review

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Abstract

Intact cognitive function is a crucial underpinning for the performance of daily activities in persons with chronic diseases, including rheumatoid arthritis (RA). Older adults with RA may have the increased burden of physical function difficulties due to the impact of both age-related cognitive decline and RA-related impairment. Population-based studies reviewed in this paper found significant cross-sectional and longitudinal relationships between cognitive function and physical function in older adults with and without comorbid health conditions. Although no study specifically examined this relationship in older adults with RA, interventions designed to enhance functional capacity by minimizing cognitive impairment may benefit older adults with RA. More studies are needed that investigate the relationship between cognitive function and physical function in older adults with RA in order to eventually improve functional status and quality of life.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that is characterized by pain, joint stiffness, joint swelling, and subsequent functional limitations and disability (Taibi & Bourguignon, 2003). The proportion of older adults living with RA has increased over time due to longevity and disease chronicity (Hootman & Helmick, 2006). Therefore, adverse outcomes in older adults with RA, such as decreased functional status, increased health care costs, increased morbidity/mortality, and decreased psychological well-being can be anticipated (Helmick et al., 2008). To minimize these outcomes, an understanding of the risk factors that aggravate functional limitations and disability could form the basis for developing effective and targeted interventions (Dunlop et al., 2005).

The purpose of this paper is to review and critique the literature exploring the relationship between cognitive function and physical function in older adults with RA. Persons with impaired cognitive function have decreased functional independence, reduced quality of life, and increased risk of mortality (Bennett et al., 2002; Neale, Brayne, & Johnson, 2001). Cognitive impairment and disability are relatively common problems that make older adults unable to live independently (Hebert, Brayne, & Spiegelhalter, 1999). For persons with chronic diseases such as RA, intact cognitive function is crucial for performing main daily activities, including adhering to medication regimens, planning and initiating activities based on one's current condition, changing plans if pain unexpectedly worsens, and inhibiting behaviors that aggravate pain or worsen health status (Abeare et al., 2010).

Cognitive function has not been extensively studied in persons with RA although

several mechanisms may influence cognitive function in these patients (Appenzeller, Bertolo, & Costallat, 2004). Only two studies have evaluated cognitive dysfunction in well characterized cohorts of RA patients using a comprehensive neuropsychological test battery that extends beyond general mental status screening exams, such as the Mini-Mental State Examination (MMSE). In one study, cognitive dysfunction was observed to be common in RA patients with prevalence rates ranging from 38% (attention and mental flexibility) to 71% (visuo-spatial and planning functions) (Bartolini et al., 2002). Additionally, Appenzeller and colleagues (2004) found cognitive impairment in 30% of the RA cohort as compared to 8% of age and sex matched healthy controls.

While these studies highlight the potential burden of cognitive impairment in RA, they are limited by several drawbacks. The sample sizes were small. Most subjects were female, white, and had low educational levels that were not representative of all RA patients. Cross-sectional study designs could not provide any cause-effect information. The use of inconsistent terms and concepts, different criteria for cognitive impairment, and disparate measures of cognitive function make it difficult to compare studies.

The relationship between global cognitive function and daily functional status has been well-studied in the general population (Reed, Jagust, & Seab, 1989; Skurla, Rogers, & Sunderland, 1988). Among the various domains of cognitive function, executive function and memory have consistently been found to be associated with everyday function, including activities of daily living (ADLs) and instrumental activities of daily living (IADLs) in older adults (Cahn-Weiner et al., 2007; Tomaszewski Farias et al., 2009). People with more impairment in executive function and memory had more functional limitations (Cahn-Weiner, et al., 2007). Additionally, longitudinal declines in

executive function and memory over time independently contributed to declines in daily function (Tomaszewski Farias, et al., 2009).

Older adults with RA may have the increased burden of functional limitations and disability in daily activities due to the impact of both age-related cognitive decline and RA-related impairment. Investigating the relationship between cognitive function and functional limitations and disability in older adults with RA may be useful for designing interventions to prevent further disability, maintain functional independence, and improve quality of life.

Methods

An online literature search was conducted to identify research articles investigating the relationship between cognitive function and physical function in older adults with RA. The PubMed, PsycINFO, and CINAHL databases were used in the search. The following combinations of terms were used in the search: "cognition, cognitive function, neurocognition, neurocognitive function, executive function, memory, memory disorder, cognitive impairment, cognitive disorder" AND "physical function, physical activity, motor activity, physical function difficulty, disability" AND "arthritis." Search inclusion criteria were articles written in English, human, and subjects aged 65 years and older.

Review articles, commentaries, and books were excluded. After reading abstracts and reviewing full articles, studies unrelated to the topic were excluded. Specifically, studies that examined subjects who already had impaired cognitive function due to neurologic disorders, such as dementia or Alzheimer's disease, or those that exclusively enrolled subjects with other types of arthritis, such as osteoarthritis or systemic lupus

erythematosus were excluded. The reference lists of relevant articles were then examined to see if they led to other works of interest. A check was made to see if there were duplicates, counting them only once.

Because there was no study which specifically assessed older adults with RA, this paper will include 27 population-based studies which examined community-dwelling, non-institutionalized older adults with several comorbid health conditions in addition to arthritis but without neurologic disorders (Table 1). The major findings, limitations, and strengths of the reviewed articles will be presented followed by the implications for future research and nursing practice.

Review and Critique of the Literature

Twelve research articles were cross-sectional studies, and 15 were prospective, longitudinal, cohort studies with observations over two or more years. The numbers of participants in the reviewed studies ranged from 80 to 7913, and most were female and white. All but four studies examined adults aged 65 years and older. One study (Appenzeller, et al., 2004) had no age restrictions. One study (Kempen & Ormel, 1998) included subjects aged 57 years and older, and two studies (Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Kuo, Leveille, Yu, & Milberg, 2007) included subjects aged 60 years and older. Only one study (Appenzeller, et al., 2004) specifically investigated RA patients. Dunlop and colleagues (2005) assessed subjects with various types of arthritis, including RA. The remaining 25 studies investigated community-dwelling, non-institutionalized, non-demented older adults with or without a wide range of chronic health conditions.

Four studies (Eggermont, Milberg, Lipsitz, Scherder, & Leveille, 2009;

Fitzpatrick et al., 2007; Rosano et al., 2005; Samper Ternent, Al Snih, Raji, Markides, & Ottenbacher, 2008) examined the relationship between cognitive function and physical function with physical function as the independent variable and cognitive function as the dependent variable. The remaining 23 studies assessed the association with cognitive function as a predictor variable and physical function as an outcome variable. The use of a wide variety of neuropsychological tests to assess cognitive function yielded confusion and complications when attempting to synthesize and compare studies. Researchers used three methodologies to assess physical function: (a) self-reported or observer-reported functional difficulties in ADLs or IADLs only (11 studies), (b) performance-based tests only (7 studies), or (c) both (9 studies). All but two (Appenzeller, et al., 2004; Kempen & Ormel, 1998) found a significant relationship between cognitive function and physical function, and other factors that might affect the association.

Studies which used subjective measures, i.e., self-reports or observer-reports of difficulties in performing daily activities, appeared to use the concept of disability (i.e., difficulty doing activities in any domain of daily life due to health problems) in the Disablement Process Model (DPM) (Verbrugge & Jette, 1994) as an outcome measure of physical function. Studies which used objective measures, i.e., performance-based tests, appeared to use the concept of functional limitations (i.e., restrictions in performing fundamental physical actions) in the DPM as an outcome measure of physical function. Similarly, studies which used both subjective and objective measures appeared to employ a combined concept of functional limitations and disability. Most studies in this review used the combined concept of functional limitations and disability as an outcome assessment of physical function, no matter what types of measures they used.

Using Subjective Measures for Physical Function Assessment

Eleven studies (Appenzeller, et al., 2004; Dunlop, et al., 2005; Eggermont, et al., 2009; Grigsby, et al., 1998; Hebert, et al., 1999; Kelly-Hayes, Jette, Wolf, D'Agostino, & Odell, 1992; Leveille et al., 1998; Moritz, Kasl, & Berkman, 1995; Raji, Al Snih, Ray, Patel, & Markides, 2004; Royall, Palmer, Chiodo, & Polk, 2004; Spiers et al., 2005) assessed self-reported or observer-reported functional difficulties in ADLs or IADLs to measure physical function. In spite of some disagreement regarding the use of self-reported data, several studies found that self-reported daily activities had high test-retest reliability even among older adults with cognitive impairment (Raji, et al. 2004; Smith et al., 1990). Some studies also found that proxy assessments of patients' abilities to perform daily activities had significant accordance with patients' assessments (Raji, et al., 2004; Weinberger et al., 1992). Therefore, subjective measures, (i.e., self-report and observer-report) may provide reliable information regarding physical function difficulties in older adults.

Only one study, by Appenzeller and colleagues (2004), examined the prevalence of cognitive impairment and risk factors for its occurrence in RA patients using a comprehensive neuropsychological test battery. Cognitive impairment was observed in 30% of RA patients and 7.5% of healthy controls. RA patients had significantly worse outcomes in verbal fluency, logic memory, and short term memory. In further analyses, cognitive impairment was not significantly correlated with disability, or with other variables, including duration of RA, current use of corticosteroid therapy, cumulative dose of corticosteroids, and neurological abnormalities (Appenzeller, et al., 2004).

This study has several limitations. The sample size was small, and all participants

were white. Most subjects were female, relatively young, and had low educational levels. Disability was assessed by only one functional classification, and it was not a primary outcome measure. However, the findings of this study have important implications, because it examined the frequency of cognitive impairment and its possible association with disability in RA patients who had not been widely investigated. In addition, possible explanations for the incidence of cognitive impairment in RA patients were offered in spite of the lack of statistically significant results.

Dunlop and colleagues (2005) examined the prevalence of functional limitations and functional decline over two years among older adults with various types of arthritis. Cognitive impairment was assessed using a general mental status screening test and memory tests as a possible predictor of functional decline. Researchers found that 19.7% of subjects had baseline functional limitations, including 12.9% with at least one ADL limitation, 5.6% with two or more, and 2.9% with three or more. Functional decline over two years was reported in 13.6% of people without severe baseline functional limitations (i.e., ≥3 ADL limitations). Lack of regular vigorous physical activity was the most prevalent risk factor. Other significant predictors for functional decline included older age, cognitive impairment, depressive symptoms, diabetes, physical limitations, no alcohol use, stroke, and vision impairment (Dunlop, et al., 2005).

The physical activity assessment did not provide specific information on the types or levels of activities in which people engaged, and whether or not people were able to perform physical activity (Dunlop, et al., 2005). As people with severe functional limitations at baseline were excluded, the predictors for functional decline were analyzed with subjects most likely to be capable of physical activities. However, the findings of

this study have important implications for public health. This study included a large population-based cohort of older adults with one of the most disabling diseases, arthritis. In addition, the finding that regular vigorous physical activity had a beneficial effect on functional outcomes is amenable to public health prevention and promotion programs.

The remaining nine studies found significant cross-sectional and longitudinal associations between poor cognitive function and physical function difficulties in community-dwelling older adults with diverse health conditions. While six studies assessed cognitive function using only a general mental screening test, mostly the MMSE, three studies (Eggermont, et al., 2009; Grigsby, et al., 1998; Royall, et al., 2004) assessed cognitive function using a set of neuropsychological tests. Eggermont and colleagues (2009) examined the relationship between physical activity and cognitive function, specifically executive function, and possible mediators. The physical activity scores were significantly associated with executive function test scores after adjusting for age, sex, education, medication use, cardiovascular disease and its risk factors, chronic pain, and depressive symptoms (Eggermont, et al., 2009).

Grigsby and colleagues (1998) evaluated the contribution of cognitive function to self-reported and observer-reported performance of ADLs and IADLs. Both general cognitive status and executive function had statistically significant associations with all physical function measures. Executive function was a predictor of self-reported performance of ADLs and observer-reported performance of IADLs. On the other hand, general cognitive status predicted only observer-reported performance (Grigsby, et al., 1998).

Royall and colleagues (2004) examined the impact of cognitive function,

especially executive function, on functional status in older adults aged 70 years and older residing in a continuing care retirement community over three years. The rate of change in Executive Interview (EXIT25) was significantly correlated with the rate of change in IADLs, adjusting for baseline EXIT25 scores, IADLs, age, comorbid disease, and level of care. The rate of change in MMSE scores was not significantly associated with the rate of change in IADLs (Royall, et al., 2004).

The findings of these studies imply that some subdomains of cognitive function (e.g., executive function) may be correlated with physical function, while others may not. A significant contribution of executive function to the prediction of functional disability even beyond that of general cognitive status was found. Therefore, assessing executive function in addition to general cognitive status may aid in the understanding of functional decline.

Using Objective Measures for Physical Function Assessment

Seven studies (Atkinson et al., 2007; Ble et al., 2005; Bootsma-van der Wiel et al., 2002; Coppin et al., 2006; Raji, Ostir, Markides, & Goodwin, 2002; Rosano, et al., 2005; Tabbarah, Crimmins, & Seeman, 2002) used a combination of various performance-based tests to assess physical function. The most frequently used test was a modified version of the Short Physical Performance Battery (Guralnik, et al., 1994) consisting of gait speed, chair rising, and standing balance tests for lower extremity function measure. Objective performance-based tests of physical function can increase validity and reproducibility, and have less bias from variations in ethnicity, culture, language, psychological mood, cognition, personality, and educational level than self-reports (Raji, et al., 2002).

Two studies (Ble, et al., 2005; Bootsma-van der Wiel, et al., 2002) assessed upper extremity function using a handgrip dynamometer in addition to lower extremity function. However, handgrip strength was not a primary outcome variable of interest but one of covariates, and the association of cognitive function with handgrip strength was not tested. Nevertheless, these studies are notable because examining both lower and upper extremity function may provide a full range of information regarding physical function.

Ble and colleagues (2005) examined the association between executive function tests and lower extremity function tasks with different executive/attentional demands in community-dwelling, non-demented older adults. After adjustment for age and sex, subjects with poor executive function compared to those with good executive function were more likely to be in the lowest tertile for the 4-meter usual pace walking speed. Subjects with poor or intermediate executive function were more likely to be in the lowest tertile for 7-meter obstacle fast pace walking speed than subjects with good executive function, adjusting for all other confounders (Ble, et al., 2005). This study has several strengths. Researchers measured two performance-based lower extremity tasks that required different executive/attentional demanding skills. They also assessed a wide variety of covariates, including sociodemographics, chronic health conditions, depressive symptoms, body mass index, and handgrip strength. Executive function was independently associated with lower extremity function that required higher executive/attentional demanding skills.

Bootsman-van der Wiel and colleagues (2002) investigated the relative effect of common chronic diseases and general impairments on walking disability in older adults

aged 85 years. The walking disability was highly associated with poor mobility in daily life, recurrent falls, and poor well-being. General impairments had higher prevalence rates, higher population attributable risks, and stronger associations with walking disability than common chronic diseases. Among general impairments, cognition and grip strength were most strongly associated with walking disability. This study has the following strengths: (a) a large sample of the oldest-old people who had not been widely studied was included, and (b) it assessed general impairments by various methods according to the International Classification of Impairments, Disabilities and Handicaps standards (Bootsma-van der Wiel, et al., 2002). The findings of this study are particularly important from a public health point of view, because general impairments in older adults are preventable and curable.

While two studies (Bootsma-van der Wiel, et al., 2002; Raji, et al., 2002) used only the MMSE, the remaining five studies (Atkinson, et al., 2007; Ble, et al., 2005; Coppin, et al., 2006; Rosano, et al., 2005; Tabbarah, et al., 2002) used a set of neuropsychological test battery to assess cognitive function. Although the latter studies did not compare the specific subdomains of cognitive function and general cognitive status, using various neuropsychological tests could add more reliable and comprehensive information than using only the MMSE. All these studies found significant cross-sectional and longitudinal relationships between cognitive impairment and physical function difficulties.

Using both Subjective and Objective Measures for Physical Function Assessment

Nine studies (Auyeung et al., 2008; Fitzpatrick, et al., 2007; Gill, Williams, Richardson, & Tinetti, 1996; Greiner, Snowdon, & Schmitt, 1996; Kempen & Ormel,

1998; Kuo, et al., 2007; Raji, et al., 2005; Samper Ternent, et al., 2008; Wang, van Belle, Kukull, & Larson, 2002) used both subjective and objective measures to assess physical function. By using both subjective and objective measures, these studies can have more reliable and less biased information regarding physical function.

Auyeung and colleagues (2008) examined the relationship between cognitive function and performance-based physical function independent of muscle mass assessed by dual-energy X-ray absorptiometry. Cognitively impaired subjects had weaker grip strengths and performed worse in the two physical function tests (i.e., 6-meter walk speed and chair stand tests). After adjusting for age, appendicular skeletal muscle mass, self-reported physical function score, and comorbid health conditions that could adversely affect the performance-based tests, cognitively impaired subjects of both genders performed consistently worse in all physical function tests (Auyeung, et al., 2008). The strength of this study is that researchers, using both subjective and objective measures, found a significant association between cognitive impairment and both poor muscle strength and physical function independent of muscle mass.

Kempen and Ormel (1998) examined the independent contribution of physical performance and cognitive status to subsequent levels of ADL disability in low-functioning older adults aged 57 years and older. Subsequent ADL disability at three years was highly predicted by both physical performance and ADL disability at baseline. ADL disability at baseline was a stronger predictor of subsequent ADL disability than impairments in baseline physical performance. Although cognitive status was slightly related to subsequent ADL disability, there were no independent contributions of cognitive status to subsequent ADL disability. There was no significant interaction effect

of physical performance and cognitive status on subsequent ADL disability (Kempen & Ormel, 1998).

Unlike most other community-based studies which examined relatively healthy older adults, this study included older adults who reported considerable physical limitations at baseline. Non-participants were older, had more chronic health conditions at baseline, and were more impaired in baseline cognitive status, physical performance, and ADL disability than participants. Therefore, the findings of this study cannot be directly compared to those of the other studies or be generalized.

The remaining seven studies found significant cross-sectional and longitudinal relationships between cognitive impairment and physical function difficulties. Three studies (Gill, et al., 1996; Raji, et al., 2005; Samper Ternent, et al., 2008) used only the MMSE, but four studies (Fitzpatrick, et al., 2007; Greiner, et al., 1996; Kuo, et al., 2007; Wang, et al., 2002) used various neuropsychological tests to obtain comprehensive information. Kuo and colleagues (2007) especially examined executive function, and investigated the association between executive function, habitual gait speed, and late-life disability in the context of the DPM (Verbrugge & Jette, 1994). Researchers found a potential mediating effect of habitual gait speed in the relationship between impaired cognitive function and disability.

Discussion

Strengths

In this review of research studies that investigated the relationship between cognitive function and physical function in older adults with and without various comorbid health conditions, several strengths deserve mention. First, many studies

examined large samples of community-dwelling, non-demented older adults with various chronic health conditions which may strengthen the generalizability of the results. Second, two studies (Bootsma-van der Wiel, et al., 2002; Hebert, et al., 1999) examined the very older population (persons aged 85 years vs. those aged 75 years and older, respectively), which is most likely to have cognitive impairment, disability, and functional dependence. The findings of these studies have significant clinical implications for assessments and interventions for this cohort, the fastest growing segment of the older population which has not been widely studied.

Third, diverse ethnic/racial groups, including Hispanics, Mexican-Americans, African-Americans, and Chinese were studied in many different countries. Fourth, 15 studies used prospective longitudinal study designs conducted over a period of 2 to 10 years. Researchers could find the cross-sectional relationship between cognitive impairment and disability, and also the longitudinal relationship between changes in cognitive function and subsequent functional decline. Fifth, the greater utility of performance-based tests in assessing physical function was found even in older adults by comparing the results of subjective and objective measures.

Sixth, most studies examined a wide range of confounding factors, including sociodemographics, depressive symptoms, comorbid health conditions, life-style behavioral factors, and pain that could affect the relationship between cognitive function and physical function. One study by Atkinson and colleagues (2007) found a mediating effect of depressive symptoms in the relationship between cognitive function and physical function. In addition, Raji and colleagues (2002) found that good emotional health status moderated the impact of impaired cognitive function on subsequent

functional difficulties. These findings imply that good emotional health may play an important role in older adults in improving functional status and maintaining independence in daily activities. Gait speed (Kuo, et al., 2007) and handgrip muscle strength (Raji, et al., 2005) measured by performance-based tests were found to be potential mediating factors in the association between impaired cognitive function and disability. The findings of these studies emphasize the effectiveness of active participation in physical exercise. Older adults may benefit from any type of physical activity in order to delay functional decline and improve physical independence.

Limitations

In spite of these strengths, there are several limitations. First, the use of diverse terms and concepts regarding cognitive function and physical function hindered researching and comparing studies. Most researchers did not specifically define the main concepts of cognitive function and physical function used in their studies. A number of terms, including cognition, cognitive function, cognitive status, neuropsychological status, general mental status, and executive cognitive function were used to represent the concept of cognitive function. The heterogeneity of criteria for classifying cognitive impairment also precluded study comparisons. Many studies followed the definitions of functional limitations and disability in the DPM (Verbrugge & Jette, 1994). However, most of the studies used both concepts interchangeably to represent the notion of physical function, and assessed them as functional outcomes. Kelly-Hayes and colleagues (1992) distinguished between the two concepts and found that disability had more social impact on an individual's daily life than functional limitations. The findings of the study by Gill and colleagues (1996) supported the DPM pathway from impairments to disability by

demonstrating the independent contributions of functional impairments to further disability and functional independence.

Second, as there is no standardized test battery for examining cognitive function, a wide range of measures was used for cognitive function assessment. Fourteen studies used only one instrument, mostly the MMSE, to assess global cognitive function. Thirteen studies used various neuropsychological tests in addition to the measurement of global mental status. Some studies (Atkinson, et al., 2007; Eggermont, et al., 2009; Grigsby, et al., 1998; Rosano, et al., 2005; Royall, et al., 2004) examined executive function in addition to global cognitive function, and found a dissociated impact of general mental status and executive function on physical function. In general, both impaired global cognitive function and executive function were associated with poor functional outcomes, with a stronger impact of executive function on physical function in older adults. Some studies (Ble, et al., 2005; Coppin, et al., 2006; Kuo, et al., 2007) which specifically assessed executive function found a significant association between impaired executive function and poor physical function. Even among studies which examined the same specific subdomain (i.e., executive function) of cognitive function, researchers used different types of neuropsychological tests that might lead to unnecessary confusion and complications in comparing study results.

Assessing executive function is important in persons with chronic diseases including RA. Executive function encompasses a set of brain processes that regulate and integrate other cognitive activities (Bryan & Luszcz, 2000). Specifically, executive function controls a group of cognitive actions such as goal planning, cognitive flexibility, selective attention, concept formation, abstract thinking, rule acquirement and adherence,

and initiating appropriate behaviors and inhibiting inappropriate behaviors (Keil & Kaszniak, 2002). Many interventions for RA often require intact executive function to make changes in knowledge, behaviors, and life-styles. Therefore, poor executive function may aggravate poor physical, psychological, and social health in persons with RA (Abeare, et al., 2010). Using only the MMSE or other global cognitive function screening tests may be insufficient and inappropriate in assessing this complex cognitive subdomain. Therefore, examining cognitive function using a set of standardized neuropsychological tests is necessary.

Third, many studies used either self-reported information or performance-based tests in assessing physical function, while few studies used both. Both self-reported and proxy-reported information on daily activities have been found to be reliable. However, Elam and colleagues (1991) found that patients, as compared to proxies, were more likely to report functional difficulties in certain ADLs. One study (Fitzpatrick, et al., 2007) found that cognitive function was significantly correlated with performance-based tests, but not with self-reported measures of disability. Using both subjective and objective measures of physical function may provide more reliable and comprehensive information in older adults who have a high risk for cognitive and physical impairment.

Fourth, most studies which used objective physical function measures only assessed lower extremity function. Only two studies (Ble, et al., 2005; Bootsma-van der Wiel, et al., 2002) assessed upper extremity function in addition to lower extremity function. However, grip strength was not a variable of interest but one of the covariates, and the association of cognitive function with grip strength was not tested. As many RA patients have fine hand-motor dysfunction, assessing upper extremity function in addition

to lower extremity function may be important in order to obtain a full range of information regarding physical function.

Finally, no study examined the relationship between cognitive function and physical function in older adults with RA. Most studies conducted secondary analyses using a large population-based sample of older adults with various chronic health conditions, including arthritis. One study by Appenzeller and colleagues (2004) specifically compared RA patients with healthy controls. However, the primary purpose of this study was not to examine the relationship between cognitive function and physical function. Rather, the researchers found the lack of association indirectly while in the process of investigating risk factors for incident cognitive impairment in RA patients. As Dunlop and colleagues (2005) examined older adults with various types of arthritis, the relationship of cognitive impairment with physical function specific to persons with RA is difficult to discern from this study.

Suggestions for Future Studies

Based on the findings, strengths, and limitations of the reviewed studies, some suggestions can be made for future studies. Most of all, it is important to use consistent and precise terms and concepts in order to avoid unnecessary confusion in comparing study findings. The development of standardized tests for the assessment of cognitive function is essential. Comparing certain subdivisions of cognitive function with global mental status would provide additional information.

Both self-reported and performance-based assessments of physical function may be needed to have more reliable and comprehensive information. A large, multiethnic/racial sample of older adults with RA should be studied. A longitudinal study

design would provide more valuable information, including causality and time-dependent factors.

Conclusion

As increasing numbers of older adults may live with RA and RA-attributable functional limitations and disability, identifying factors that exacerbate or enhance physical function is an important initial step for its effective management. Older adults with RA may benefit from preventive intervention programs designed to decrease aggravating factors such as cognitive impairment or depression, and to increase promoting factors such as exercise or good emotional health. More studies should investigate the relationship between cognitive function and physical function in older adults with RA in order to eventually improve functional status, independence, and quality of life.

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Table 1. Summary of Literature Review of the Relationship between Cognitive Function and Physical Function in Older Adults with RA

Reference	Sample	Design	Variables	Measures	
				Cognitive Function	Physical Function
Using Subjective Measures for Physical Function Assessment (N = 11)					
Appenzeller, Bertolo, & Costallat (2004)	*N* = 80 Patients with RA (*n* = 40) were compared to age and sex matched healthy controls (*n* = 40) in Brazil	Cross-sectional study	**IV** •Cognitive impairment **DV** •Disability	•MMSE •Logic memory tests •Short and long memory tests •Verbal fluency tests •Attention tests	•Functional classification of Steinbrocker
Dunlop, et al. (2005)	*N* = 5715 Older adults aged 65 years and older with arthritis from the Health and Retirement Study	Prospective longitudinal study	**IV** •Cognitive function **DV** •Functional limitations •Functional decline	•A modified version of the Telephone Interview for Cognitive Status •Immediate and delayed verbal recall tests •Serial 7's test	•Functional limitations in IADLs or ADLs •Functional decline: 2-year progression to a more severe level of functional limitations
Eggermont, Milberg, Lipsitz, Scherder, & Leveille (2009)	*N* = 544 Community-dwelling older adults aged 70 years and older residing in Boston area from the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly Boston Study	Cross-sectional study	**IV** •Physical activity **DV** •Cognitive function	•Letter fluency and category fluency tests •TMT Part A and B •Clock-in-a-Box Test •Hopkins Verbal Learning Test-Revised	•Physical Activity Scale for the Elderly
Grigsby, Kaye, Baxter, Shetterly, &	*N* = 1158 Community-dwelling persons aged 60-99 years	Cross-sectional study	**IV** •General mental status •Executiv	•MMSE •Behavioral Dyscontrol Scale	•An abbreviated version of the Structured Assessment of Independent Living

Hamman (1998)	who were Hispanics (*n* = 637) or non-Hispanic whites (*n* = 521) from the San Luis Valley Health and Aging Study		e function **DV** •Physical function		Skills •Self-reported performance of daily tasks in seven ADLs and eight IDLs
Hebert, Brayne, & Spiegelhalter (1999)	*N* = 504 Community-dwelling older adults aged 75 years and older living in Sherbrooke, Quebec, Canada	Prospective longitudinal study	**IV** •Cognitive status **DV** •Functional decline •Functional improvement	•A modified MMSE	•Functional Autonomy Measurement System
Kelly-Hayes, Jette, Wolf, D'Agostino, & Odell (1992)	*N* = 1453 Community-dwelling older adults living in Framingham, MA from the Framingham Study	Cross-sectional study	**IV** •Cognitive function **DV** •Disability •Functional limitations	•MMSE	•Self-reported disability questionnaire in six ADLs from the Katz and Mahoney and Barthel indexes •Observed functional limitations
Leveille, et al. (1998)	*N* = 3585 Community-dwelling women (whites = 2694, blacks = 891) aged 65 years and older with MMSE≥18 living in East Baltimore, MD from the Women's Health and Aging Study	Cross-sectional study	**IV** •Cognitive function **DV** •Functional difficulties	•MMSE	•Functional difficulties in ADLs, IADLs, and mobility (walking two or three blocks and climbing 10 steps without resting)
Moritz, Kasl, & Berkman	*N* = 1865 Community-dwelling	Prospective longitud	**IV** •Cognitive function	•Pfeiffer's Short Portable Mental Status	•A modified version of the Katz ADL Scale

(1995)	older adults aged 65 years and older living in New Haven, CT who were initially free of ADL limitations from the Yale Health and Aging Project	inal study	**DV** •Persistent incident ADL limitations	Questionnaire	•Rosow-Breslau Scale
Raji, Al Snih, Ray, Pate, & Markides (2004)	*N* = 2731 (non-ADL disabled at baseline = 2431) A population-based sample of Mexican-Americans aged 65 years and over from the Hispanic Established Populations for the Epidemiologic Study of the Elderly	Prospective longitudinal study	**IV** •Cognitive function **DV** •Functional disability	•MMSE	•A modified version of the Katz ADL scale
Royall, Palmer, Chiodo, & Polk (2004)	*N* = 547 Older adults aged 70 years and older residing in a continuing-care retirement community, the Air Force Villages, from the Freedom House Study	Prospective longitudinal study	**IV** •Executive control function **DV** •Functional status	•MMSE •Executive Interview	•Older Adults Resources Scale: self-reported information on ADLs, IADLs, health history, health care use, and current medications
Spiers, et al. (2005)	*N* = 7913 Older adults	Prospective	**IV** •Cognitiv	•MMSE	•A modified Townsend ADL

	aged 65 years or older in five urban and rural centers in England and Wales from the Medical Research Council Cognitive Function and Ageing Study	longitudinal study	e function **DV** •Disability		scale covering nine ADLs/IADLs •Interviewer's rated mobility
Using Objective Measures for Physical Function Assessment (N = 7)					
Atkinson, et al. (2007)	*N* = 2349 Nondisabled, well-functioning black and white older adults aged 70-79 years residing in Pittsburgh, PA and Memphis, TN from the Health, Aging and Body Composition Study	Prospective longitudinal study	**IV** •Global cognitive function •Executive control function **DV** •Gait speed decline	•A modified, expanded version of the MMSE •Clock drawing task •15-item Executive Interview	•20-meter gait speed test
Ble, et al. (2005)	*N* = 926 Community-dwelling older adults aged 65 years and older without dementia, stroke, Parkinsonism, visual impairment, or current treatment with neuroleptics residing in	Cross-sectional study	**IV** •Executive function **DV** •Lower extremity function	•MMSE •TMT Part A and B	• 4-meter usual pace walking and 7-meter obstacle fast pace walking tests •Handgrip dynamometer

	Greve, Chianti and Bagno, Ripoli, in Italy from the InChianti Study				
Bootsma-van der Wiel, et al. (2002)	*N* = 599 Older adults aged 85 years from the Leiden 85-plus Study in the Netherlands	Cross-sectional study	**IV** •Cognitive impairments **DV** •Walking disability	•MMSE	•6-meter walking test •Difficulties walking (indoors/outdoors/stairs), part of the Groningen Activity Restriction Scale •Handgrip dynamometer
Coppin, et al. (2006)	*N* = 737 Community-dwelling non-demented older adults aged 65 years and older residing in Greve, Chianti and Bagno, Ripoli,in Italy from the InChianti Study	Cross-sectional study	**IV** •Executive cognitive function **DV** •Physical performance	•MMSE •TMT Part A and B	•Gait speed tests: Complex vs. reference walking tests
Raji, Ostir, Markides, & Goodwin (2002)	*N* = 2068 Community-dwelling Mexican Americans aged 65 years and older with MMSE scores ≥18 at baseline and complete data on a summary performance measure at 2-year follow-up from the	Prospective longitudinal study	**IV** •Cognitive function •Emotional health **DV** •Lower body function	•MMSE •CES-D	•The summary performance measure of lower body function: A timed 8-foot walk, rising from a chair five times, and a hierarchical standing balance task

	Hispanic Established Population for the Epidemiological Study of the Elderly				
Rosano, et al. (2005)	*N* = 2893 Well-functioning, nondisabled black and white older adults aged 70-79 years residing in Pittsburgh, PA and Memphis, TN from the Health, Aging and Body Composition Study	Cross-sectional study	**IV** •Physical function **DV** •Cognitive function	•Teng-modified MMSE •Digit symbol substitution test	•Gait speed tests: 6-meter usual walk and narrow walk •Repeated chair stand tests •Standing balance test
Tabbarah, Crimmins, & Seeman (2002)	*N* = 488 High-functioning, disability-free older adults aged 70-79 years from the MacArthur Research Network on Successful Aging Community Study	Prospective longitudinal study	**IV** •Cognitive performance **DV** •Physical performance	•The sum of the performances on five subscales (spatial memory, similarity of abstract concepts, language, delayed verbal memory, and spatial orientation) •Delayed Span Test •Boston Naming Test •Wechsler Adult Intelligence Scale-Revised •Drawing test	•Five routine physical tasks •Six novel/attentional demanding physical tasks
Using both Subjective and Objective Measures for Physical Function Assessment (N = 9)					
Auyeung, et al. (2008)	*N* = 4000 Community-dwelling Chinese elderly aged 65 years and older	Cross-sectional study	**IV** •Cognitive function •Muscle strength •Muscle mass **DV**	•The cognitive part of the Chinese version of the Community Screening Instrument of Dementia	•Dual-energy X-ray absorptiometry (whole body muscle mass and appendicular skeletal muscle mass) •Grip strength •Chair stand tests

			•Physical function		•6-meter gait speed •Physical Activity Scale for the Elderly
Fitzpatrick, et al. (2007)	*N* = 3035 High-functioning, non-demented older adults aged 75 years and older from the Ginkgo Evaluation of Memory Study	Cross-sectional study	**IV** •Physical function **DV** •Cognitive function	•Telephone Interview for Cognitive Status questionnaire •A modified MMSE •14 neuropsychological tests	•Self-reported ADLs and IADLs •Mobility •Upper extremity strength •Difficulties in walking a half mile •15-foot usual and rapid pace walk tests
Gill, Williams, Richardson, & Tinetti (1996)	*N* = 945 Community-dwelling persons aged 72 years and older from the Project Safety cohort living in New Haven, CT, who were nondisabled at baseline	Prospective longitudinal study	**IV** •Cognitive status •Physical performance **DV** •Functional dependence in ADLs	•MMSE	•Seven items from a modified version of the Katz ADL Scale •A composite measure of physical performance: Walking back and forth over a 10-foot course, turning in a full circle, and standing up/sitting down from a hard-back chair three times with arms folded
Greiner, Snowdon, & Schmitt (1996)	*N* = 678 Elderly nuns who completed cognitive and physical function tests from the Nun Study of Alzheimer's disease and aging	Prospective longitudinal study	**IV** •Cognitive function **DV** •Physical function	•Neuropsychological tests •MMSE	•Self-reported ADLs •Performance-based ADLs from the Performance Test of Activities of Daily Living, the Simulated Activities of Daily Living Examination, and a modified version of the Blessed Dementia Scale
Kempen & Ormel (1998)	*N* = 753 Community-dwelling older adults aged 57 years and older who	Prospective longitudinal study	**IV** •Cognitive status •Physical performance **DV**	•MMSE	•Physical performance tests: Putting on/off a jacket, walking six meters including a 180 degree turn after three meters, and

	reported substantial physical limitations from the Groningen Longitudinal Ageing Study in the Netherlands		•ADL disability		five chair standing tests •Physical functioning scale of the Short Form-20 General Health Survey •11-item ADL subscale of the Groningen Activity Restriction Scale
Kuo, Leveille, Yu, & Milberg (2007)	*N* = 2481 Older adults aged 60 years and older from the National Health and Nutrition Examination Survey	Cross-sectional study	**IV** •Cognitive function including executive function •Habitual gait speed **DV** •Disability in ADL, IADL, leisure/social activities, and lower extremity mobility	•2-minute timed Digit Symbol Substitution Test, a component of the Wechsler Adult Intelligence Test and a test of visuo-spatial and motor speed-of-processing	•12-item Physical Functioning Questionnaire: Difficulty in ADL, IADL, leisure/social activities, and lower extremity mobility •20-foot timed walk test
Raji, et al. (2005)	*N* = 2281 Community-dwelling Mexican-Americans aged 65 years and older with no ADL disability at baseline from the Hispanic Established Population for the Epidemiological Study of the Elderly	Prospective longitudinal study	**IV** •Cognitive function **DV** •Change in handgrip muscle strength •Incidence of functional disability	•MMSE	•A hand-held dynamometer •A modified version of the Katz ADL Scale
Samper-Ternent, Al Snih, Raji,	*N* = 1370 Community-dwelling	Prospective longitud	**IV** •Frailty **DV**	•MMSE	•Frailty Index: Unintentional weight loss of >10 pounds,

Markides, & Ottenbacher (2008)	Mexican-Americans aged 65 years and older with MMSE scores ≥21 at baseline from the Hispanic Established Population for the Epidemiological Study of the Elderly	inal study	•Cognitive function		lowest 20% in grip strength using a hand-held dynamometer, two self-reported exhaustion items from the CES-D, lowest 20% in 16-feet walk-time, and lowest 20% in Physical Activity Scale for the Elderly score
Wang, van Belle, Kukull, & Larson (2002)	*N* = 2581 Cognitively intact older adults aged 65 years and older from the Group Health Cooperative members in Seattle in the Adult Changed in Thought Study (mean follow-up time = 3.4 years; range = 0-7 years)	Prospective longitudinal study	**IV** •Cognitive function **DV** •Functional status •Functional decline	•Cognitive Abilities Screening Instrument •Memory and general function evaluation •Three Reaction Time-simple and choice reaction time test	•Self-reported ADLs and IADLs •Performance-based Physical Function Testing:10-foot timed walk, five repeated chair stand time, standing balance, and grip strength (dominant hand)

RA: Rheumatoid arthritis/ IV: Independent variable/ DV: Dependent variable/ ADLs: Activities of daily living/ IADLs: Instrumental activities of daily living/ MMSE: Mini-Mental State Examination/ CES-D: Center for Epidemiological Studies Depression/ TMT: Trail Making Test

Chapter 3: Theoretical Framework

Paper 2: Disability Intervention Model for Older Adults with Arthritis: Incorporating the Disablement Process Model and the Theory of Symptom Management

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Abstract

The initial step for rheumatoid arthritis (RA) management is to properly understand a patient's disablement process and symptom experience. A Disability Intervention Model for Older Adults with Arthritis (DIMOA) has been constructed based upon the broad concepts of the Disablement Process Model (DPM) and the Theory of Symptom Management (TSM) which address the extensive aspects of an individual's disablement process and symptom management. By incorporating the DPM into the TSM, the DIMOA can help in the understanding of the disabling experience in individuals with RA, management strategies, and subsequent outcomes that should not be omitted. Therefore, the DIMOA can be utilized as a guiding theoretical framework for arthritis research to improve functional status in older adults with RA.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that is characterized by pain, joint stiffness/swelling, fatigue, and subsequent functional limitations and disability (Taibi & Bourguignon, 2003). The average age of persons with RA and the proportion of older adults with RA have increased over time due to longevity and disease chronicity (Helmick et al., 2008). This suggests that RA-related adverse effects on functional status, health care costs, morbidity/mortality, and psychological well-being may increase as well. Considering the rapid increase in the older population, the impact of RA may be an important public health issue.

Because RA is a chronic, incurable disease, the ultimate goals for its management are to control pain, minimize joint damage, maintain function, and improve quality of life (Hootman & Helmick, 2006). According to the American College of Rheumatology (ACR, 2002), early diagnosis, proper evaluation, and prognosis prediction are crucial steps for effective RA management. The ACR guidelines emphasize patient education (e.g., self-care, exercise, and lifestyle changes) with supportive care as one of the most important interventions for optimal management of RA in addition to conventional pharmacological therapies. To achieve these goals, a comprehensive understanding of a patient's symptom experience from his/her perspective, development of effective management strategies, and proper evaluation of subsequent outcomes is essential. In addition, identifying potential interactions among these factors and assessing contextual variables that may affect the symptom experience, interventions, and outcomes are indispensable.

The Theory of Symptom Management (TSM) (Humphreys, et al., 2008) has been

utilized in many studies to understand a patient's symptom experience, management, and outcomes. It is a comprehensive model which includes a wide range of concepts and other contextual variables within three key dimensions of nursing science, person, environment, and health/illness. However, to our knowledge, no study has applied or tested the TSM with arthritis patients. The Disablement Process Model (DPM) (Verbrugge & Jette, 1994) addresses the influence of a disease, other contextual variables, and the relationships among them on functioning. The simplicity and practicability of the DPM make it easy to apply as a conceptual framework for many research studies in persons with various health conditions including arthritis, but also may limit its ability to fully capture a patient's disabling symptom experience and management.

Because the TSM encompasses the key concepts of the DPM, the incorporation of constructs from the DPM into the TSM may provide a more comprehensive framework that can facilitate an understanding of the disablement process and symptom management, as well as guide arthritis care and research. Therefore, the purpose of this paper is to introduce and critique the two models as a conceptual foundation from which to construct a Disability Intervention Model for Older Adults with Arthritis (DIMOA).

Theory of Symptom Management

The TSM was first introduced by the symptom management faculty group at the University of California, San Francisco (UCSF) School of Nursing in 1994 (Larson et al., 1994). The concept labels and their interrelationships in the symptom management model were revised in 2001 (Dodd, et al., 2001), and the TSM was proposed in 2008 as a middle range theory for nursing (Humphreys, et al., 2008). The TSM comprises three essential components, namely the symptom experience, symptom management strategies, and

symptom outcomes. Dynamic relationships among these concepts are placed within a three-dimentional sphere of person, environment, and health/illness which are the main domains of nursing science.

The Main Concepts

A symptom refers to "a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual," while a sign is "any abnormality indicative of disease that is detectable by the individual or others" (Humphreys, et al., 2008, p. 145). A symptom is a more patient-centered concept that may affect a patient's daily life by disrupting all domains of functioning.

Symptom experience is a dynamic interaction comprising an individual's perception, evaluation, and response to a symptom (Humphreys, et al., 2008). When people notice unusual feelings (perception), they assess the characteristics of their symptom, including severity, location, duration, frequency, cause, curability, and its disabling effect (evaluation). People, then, try to relieve their symptoms by developing their own self-care strategies or seeking health care for more effective interventions (response). Symptom experience should be understood as a personal and multidimensional feature of an individual and a dynamic interaction among the three factors of symptom experience.

Symptom management strategies aim to avert, delay, or minimize the symptom experience, and its negative outcomes (Humphreys, et al., 2008). In order to achieve the goal of symptom management, the specifications of who, where, how much, when, as well as what the intervention strategy involves should be considered (Humphreys, et al., 2008). When people experience a symptom, they often try several self-care strategies first.

If they fail to manage their symptoms with self-care strategies, they may seek health care providers to receive more formalized and advanced medical treatments (what). Even simple self-care strategies or other regimens may be more effective if a patient can get support from family caregivers or other health care providers (who). In the same context, the effect of mangement strategies may differ by the enviroment (where), i.e., where such intervention is administered, for example, at home, in hospital settings, or at other institutions. The dose (how much) and the timing (when) of interventions are also important to effectively manage symptom experience. In the case of RA, for example, when a person tries exercise to improve joint function, the duration, intensity, and frequency of exercise are as important as what exercise is performed.

Symptom outcomes following the implementation of symptom management strategies are measurable. If the strategies are effective, patients may have positive outcomes, including improvement in functional status, emotional status, self-care ability, costs, quality of life, morbidity, and mortality (Humphreys, et al., 2008).

The three core concepts of the TSM are continuously interacting with each other, and the bidirectional arrows in the model show this dynamic relationship (Humphreys, et al., 2008). The symptom experience may affect or be affected by management strategies and outcomes. As people recognize symptoms, they may implement several management strategies, and assess outcomes. According to the outcomes, their symptom perceptions will be affected, and their management strategies may change. As symptom experience and management strategies are adjusted or changed, their outcomes will be affected. This process may continue repeatedly until symptoms subside or are resolved (Humphreys, et al., 2008).

The symptom management process may be interrupted, however, if there is a problem with adherence (Humphreys, et al., 2008). If the prescribed strategy is not accepted or utilized at all, or is applied inconsistently, nonadherence may become a challenging issue. A broken arrow is placed in the model between the management strategies and outcomes to acknowledge this concern. The factors in the person, environment, or health/illness domains may additionally influence nonadherence in symptom management (Humphreys, et al., 2008).

The Domains of Person, Environment, and Health/Illness

The three main concepts of the TSM are influenced by the surrounding domains of person, environment, and health/illness. Person variables include demographic, physiological, psychological, sociological, and developmental factors which are intrinsic to an individual (Dodd, et al., 2001). These factors often play a role as predisposing or risk factors which may affect an individual's views, attitudes, and behaviors. The domain of environment is the collective milieu where a symptom occurs, including physical (e.g., home, work, or hospital), social (e.g., social network or interpersonal relationships), and cultural (e.g., beliefs, values, attitudes, or behaviors) aspects (Dodd, et al., 2001).

The health/illness domain consists of health or illness status, risk factors, diseases or injuries, and disabilities that directly or indirectly affect an individual's symptom experience, management strategies, and outcomes (Dodd, et al., 2001). In summary, the contextual factors situated in the three domains of person, environment, and health/illness influence or are influenced by the three major components of the TSM by multidirectional interactions.

Applications of the TSM in Arthritis Research

The TSM has been utilized in many symptom research studies with diverse populations, including people with asthma (Hardie, Janson, Gold, Carrieri-Kohlman, & Boushey, 2000) or HIV (Tsai, Hsiung, & Holzemer, 2002). To date, however, no study has been conducted that has applied or tested the TSM with arthritis patients. In fact, only a few studies have explored the symptom experience of persons with arthritis, how they self-manage their symptoms, and the relationship between self-management and functional outcomes. Although the use of the TSM was not explicitly addressed, most of these studies indeed had ideas analogous with those of the TSM.

Radford et al. (2008), for example, interviewed patients with recently diagnosed RA (5-8 months) and patients with more than 5 years of disease duration regarding the medical care they received at first diagnosis, and the most helpful support they expected to receive. Four themes emerged: (a) information (symptoms, management strategies, and outcomes), (b) support (emotions, safe environment, and family), (c) choice (talking to other patients or health care providers), and (d) involvement (holistic care, partnership, and joint decisions) (Radford, et al., 2008). Information and support overlapped indicating patients' needs for talking and being listened to. Choice and involvement also overlapped implying proper timing and options for interventions (Radford, et al., 2008). The findings of this study suggest potential interventions that could benefit newly diagnosed RA patients. The issue of when and how to provide them should also be considered to enhance their efficacy.

Many researchers have evaluated the effect of the Arthritis Self-Management Program (ASMP), a program that has been widely recommended by many national institutions and organizations. The ASMP is a small-group, community-based, self-

management educational program developed and evaluated by Lorig and colleagues at Stanford University. The ASMP has been found to decrease pain and depression, increase physical activity, and decrease physician visits (Goeppinger et al., 2009; Lorig, Ritter, Laurent, & Fries, 2004; Lorig, Ritter, Laurent, & Plant, 2008). Lorig and researchers from many different countries have evaluated the effect of this self-management program (management strategies) by assessing baseline pain, fatigue, functional limitations, and disability (symptom experience) and changes in self-efficacy, health status, health behaviors, and health care use (outcomes). Although none of these studies explicitly utilized the TSM in their studies, the underpinning theoretical background appears to be in accordance with the TSM. Therefore, the TSM might be a good fit for these studies.

Limitations of the TSM

The original TSM focused on a single symptom, but the symptom experience may involve several symptoms as a group. Symptom clusters, three or more concurrently occurring symptoms that are associated with each other, may have an adverse and synergistic effect on patient outcomes (Dodd, Miaskowski, & Lee, 2004; Dodd, Miaskowski, & Paul, 2001). These various symptoms may interact with each other, and bring unanticipated consequences to a person's symptom experience, management strategies, and outcomes.

The TSM also does not clearly address the influence of the temporal component of time (Brant, et al., 2010; Humphreys, et al., 2008). As acute symptom manifestations are largely different from chronic ones, and a patient's subjective symptom experience may change over time, assessing the symptom experience or selecting symptom management strategies may become more complicated.

The adherence factor may affect all three components as well as the domains of person, environment, and health/illness (Donesky-Cuenco, Janson, Neuhaus, Neilands, & Carrieri-Kohlman, 2007). The adherence component may be affected by the personal characteristics of the patient, the desirability of the interventions to the patient, or the outcomes of specific interventions. Therefore, placing the adherence element between the management strategies and outcomes may be too restrictive (Humphreys, et al., 2008).

The TSM, which is a patient-centered, individualized model for symptom management, does not explicitly address the role of family caregivers or health care providers. Symptom management is not just an individual's responsibility, but is also a central task for family caregivers and health care providers. In particular, older adults with multiple chronic conditions may need more support from family caregivers or health care providers due to the unique features related to aging.

Finally, as a minor issue, it is somewhat difficult to determine where certain variables should be placed within the model. For example, some crossover concepts exist in both the person and environment domains, i.e., physical, social and cultural elements, can be included in both domains.

Strengths of the TSM

In spite of these limitations, the TSM has several strengths. Because the TSM is a very comprehensive and patient-centered model, the TSM can be utilized as a guiding theoretical framework for both research and clinical practice with diverse populations. The TSM leads both researchers and clinicians to be able to explore the symptom experience from a patient's perspective, to develop effective management strategies, and to evaluate symptoms as an outcome following the interventions.

The TSM clearly addresses the dynamic interrelationships among and within the concepts (Brant, Beck, & Miaskowski, 2010). The concept of symptom experience includes not only the patient's unique and personal symptom perception and evaluation, but also his/her actual response to the strain that the symptom may cause. The TSM implies the important role of a patient in symptom management according to his/her distinctive symptom experience. It suggests the potential responsibilities of family caregivers and health care providers in the development, implementation, and evaluation of symptom management. The TSM also addresses various outcomes, including general health outcomes such as functional status, health care use, and morbidity/mortality, and global health outcomes such as quality of life.

The concept of adherence aids in evaluating the impact of interventions on various aspects of the symptom experience and outcomes. This is because it emphasizes how a patient's readiness, motives, activeness, or confidence leads to successful symptom management and outcomes. The notion of adherence supports the importance of social support and other forms of medical care which are designed to encourage a patient's motivation and self-efficacy.

Disablement Process Model

The DPM, first proposed by Verbrugge and Jette (1994), describes: (a) how medical conditions affect functioning in particular body systems, physical and mental actions, and daily activities, and (b) how personal and environmental factors exacerbate or retard the disablement process. Four concepts, pathology, impairments, functional limitations, and disability, consist of the main pathway of the DPM.

The Main Pathway

Pathology refers to biomedical or physiological abnormalities that are classified as disease, injury or congenital/developmental conditions (Verbrugge & Jette, 1994). As biomedical or physiological abnormalities are not always directly measurable, pathology is often detected indirectly by evaluating signs and symptoms. Impairments are dysfunctions and structural abnormalities in specific body systems that can impact physical, mental, or social functioning (Verbrugge & Jette, 1994). Impairments can be evaluated by various medical procedures, including clinical examinations, laboratory tests, imaging procedures, medical history, signs, and symptoms. Functional limitations are restrictions in performing fundamental physical and mental actions employed in daily life (Verbrugge & Jette, 1994). Physical and mental actions can be assessed by: (a) self-reports or proxy-reports of trouble performing an action, and (b) performance-based measures assessed by an interviewer's ratings and timed tasks.

Disability refers to difficulty doing activities in any domain of daily life due to health problems (Verbrugge & Jette, 1994). Daily life activities can be classified into three categories: (a) obligatory activities, which are necessary for a person's survival and self-sufficiency, (b) committed activities, which are for a person's productive social roles and household management, and (c) discretionary activities, which are for a person's free-time pursuits, relaxation, and pleasure (Verbrugge, 1990; Verbrugge & Jette, 1994). A comprehensive evaluation of all domains of human activities that are meaningful to individuals is crucial in assessing disability. Disability can be measured by self-reports or proxy-reports by interviewing individuals about the degree of difficulty.

Risk Factors, Interventions, and Exacerbators

According to the DPM, the main pathway from pathology to disability may be

affected by a variety of contextual factors, including risk factors, interventions, and exacerbators. Risk factors, also known as predisposing factors, include demographic, lifestyle, biological, behavioral, psychological, social, and environmental characteristics of an individual that may increase the possibility of the occurrence and severity of impairment, functional limitation, and disability (Verbrugge & Jette, 1994).

Interventions by individuals or other health care providers attempt to avoid or delay the disablement process, and are often multiple and changeable. Interventions include: (a) extra-individual factors, such as medical care and rehabilitation, medications and other therapeutic regimens, external support, and environment modifications, and (b) intra-individual factors, such as lifestyle and behavioral changes, psychological attributes and coping, and activity accommodations (Verbrugge & Jette, 1994).

Exacerbators may occur indirectly when interventions work inappropriately or unexpectedly. For example, medical procedures and medications may have adverse effects that make conditions even worse. In response to their health problems, people sometimes adjust behaviors or lifestyles inappropriately, or adopt behaviors or attitudes that may actually increase their limitations and disability. Sometimes, because of predisposing environmental or social impediments (e.g., inflexible working hours, architectural barriers, or social prejudice) people cannot do what they want or what they are able to do (Verbrugge & Jette, 1994).

Applications of the DPM in Arthritis Research

The DPM has been utilized and tested in many disability studies, including studies of individuals with arthritis. According to the authors, the concepts of the DPM provide a guiding framework for constructing a research design as well as for applying

study findings to patient care, public health, and health policy (Verbrugge & Jette, 1994). Some researchers explicitly mention the use of the DPM as a conceptual foundation for their studies, while others modify or expand it to construct their own study models for specific health conditions.

Escalante and del Rincon (1999) adopted the DPM to investigate the proportion of disability in RA patients that could be explained by the factors in the DPM. Overall, 33% of the variance in disability was explained by the main pathway factors, of which 14% was explained by signs and symptoms as a group (i.e., tender/deformed joint count, and morning stiffness). Contextual factors explained 26% of the variance in disability, of which 20% was explained by psychological status (i.e., learned helplessness, self-efficacy, and depression). This study found that both the main pathway and external variables considerably affected the functional outcomes of RA. Signs and symptoms were found to have a stronger influence on disability than the disease per se. The importance of psychological factors was supported because of the relatively stronger impact on disability than the disease or its manifestations.

Katz, Morris, and Yelin (2006) identified the prevalence and predictors of disability in 26 valued life activities (VLAs) covering obligatory, committed, and discretionary activities in RA patients based on the DPM. VLA disability was found to be common in RA patients, with greater disability in committed and discretionary activities as compared to obligatory activities. Disease status measures, including symptoms, were strong predictors of VLA disability, explaining 22-45% of the total variance in VLA disability. The functional limitations score appeared to mediate the effect of disease status measures on disability, and was a strong predictor of VLA disability (Katz, et al., 2006).

This study has important implications in that it assessed a wide spectrum of activities, including obligatory, committed, and discretionary activities, and supported the predicted pathway proposed in the DPM. The authors found that disease status measures, including symptoms, were strongly related to functional outcomes. This implies that assessing symptoms of RA patients may be useful for predicting outcomes. As disability may further influence a person's psychological well-being and quality of life (Katz, 2004; Katz & Yelin, 1995), identifying predictors of disability in VLAs should be emphasized as an important assessment approach.

Limitations of the DPM

As initially described by Verbrugge and Jette (1994), the DPM does not sufficiently encompass the dynamic and varied aspects of life-long disability and late-life disability, or differentiate their unique impacts on a patient's disabling experience in daily life. Although Verbrugge and Jette (1994) mentioned the feedback effects and bidirectional relationships among the main components, the DPM still looks linear, and may miss the underpinning dynamic actions in the disablement process. Researchers have also addressed the concept of global outcomes beyond disability, such as well-being and quality of life, but this has not been reflected within the main pathway of the DPM yet. Users of the DPM may unintentionally miss or ignore these critical outcomes. As disability may further influence a person's psychological well-being and quality of life (Katz, 2004; Katz & Yelin, 1995), inclusion of additional outcomes in the main pathway might be helpful in order to comprehensively understand the disablement process and develop the most effective intervention.

Strengths of the DMP

In spite of some limitations, the DPM has been utilized in many studies because of its comprehensiveness and practicality. The DPM pays attention to medical and social aspects of disability by expanding its conceptual scope to assess diverse forms of activities in a person's daily life. It encompasses person and environment and their interactions in a socio-cultural context. It elaborates not only the main pathway from pathology to disability, but also intrinsic and extrinsic risk factors, interventions, and exacerbators which may affect the disablement process. The DPM extends the conventional perspectives of medical, epidemiological, and public health, i.e., from medical cure to preventive care. Finally, this model leads researchers to focus on diverse aspects of functional outcomes, such as physical, psychological, and socio-cultural, as well as further global outcomes, such as psychological well-being and quality of life.

Disability Intervention Model for Older Adults with Arthritis

With a comprehensive understanding of the concepts, applications, strengths, and limitations of the two models, a DIMOA has been created (Figure 1). The DIMOA is essentially based on the TSM, with an effort to incorporate key components of the disablement process of RA into the TSM so that it can be utilized as a theoretical foundation specifically for RA management in research and clinical practice.

The DIMOA includes the three interrelated concepts of symptom management (i.e., symptom experience, symptom management strategies, and symptom outcomes) that correspond to the TSM. These main concepts influence or are influenced by contextual factors that are situated within the three domains of nursing science (i.e., person, environment, and health/illness). The DIMOA accepts the bidirectional, complex, dynamic interactions among all components within the model representing the

comprehensive aspects of the disablement process and its interventions in older adults with RA.

Conceptually, the components of pathology and impairments from the DPM fall within the symptom experience dimension, while functional limitations may be conceptualized within the symptom experience or the symptom outcomes dimension depending on the duration and severity of the disease or symptoms and the assessment time point. For example, older adults who have suffered from RA for a long time or those in the flare-up stage may have experienced various devastating disabilities. On the other hand, persons who have undergone relatively short-term symptoms or those in the remission period, may have some functional limitations, but have not proceeded to the disability stage. As disability encompasses physical, cognitive, and emotional aspects of a person's health status that may affect his/her psychological well-being and quality of life, it should be assessed as one of the most important symptom outcomes. By incorporating the concepts of illness trajectory into the model, the DPM begins to address the temporal aspects of a chronic illness that are less evident in the TSM.

The contextual variables of the DPM, including risk factors, intra- and extra-individual intervening and exacerbating factors, are all addressed in the TSM as dynamically interrelated domains of person, environment, and health/illness. These various factors may affect or be affected by a person's symptom experience (pathology and impairments), management strategies, and outcomes (functional limitations and disability) that also interact with each other. The contextual domains of person, environment, and health/illness are depicted in the DIMOA as in the TSM, reflecting the dynamic interactions among all domains within the model.

As the TSM is a patient-centered, individualized model, the role of health care providers and the importance of medical treatments for symptom management are not explicitly depicted. On the other hand, these are clearly presented as extra-individual factors in the DPM. The DPM shows how a patient plays an active role in the symptom management process by performing self-care and coping, changing lifestyles or behaviors, accepting medical care and external support, and modifying physical and social environments. The DPM also shows how others, including family caregivers or health care providers, contribute to a person's symptom management as indispensible collaborators and supporters. Therefore, self-care/coping skills, social support, as well as conventional pharmacological treatments are included in the DIMOA under the dimension of symptom management strategies.

While the adherence component is placed between symptom management strategies and outcomes in the TSM, it is depicted in the middle of the DIMOA. This is because, as mentioned earlier, the adherence component may affect or be affected by all three dimensions, such as symptom characteristics, desirability of the interventions, or health outcomes, as well as their interactions within the model.

Global outcomes (e.g., hospitalization, institutionalization, death, happiness, life satisfaction, and well-being) which may be caused by the long-term disability experience were additionally addressed, but not clearly depicted in the main pathway of the DPM. In the DIMOA, all of these outcomes can be explained and evaluated as symptom outcomes which include a person's various aspects of health status (physical/cognitive/emotional), quality of life, health care use/costs, and morbidity/mortality.

Limitations and Strengths of the DIMOA

Although the DIMOA has been generated to compensate for the aforementioned drawbacks of the DPM and the TSM, it may still have some limitations to be tested in research studies. Understanding the main concepts within a dynamic, three-dimensional sphere of the domains of person, environment, and health/illness may be challenging. In addition, confusion or complexity may still exist because of a few variables and certain factors that can be included in one or more domains due to their overlapping concepts.

In spite of some possible drawbacks, the DIMOA has potential strengths. It encompasses the majority of the concepts of the DPM and the TSM that have been used and tested directly or indirectly in many studies. It attempts to compensate for the limitations of the two models, and aims to understand the impact of RA on a patient's physical, cognitive, and emotional health status, socioeconomic aspects, and well-being. Therefore, the DIMOA can be used as a guiding theoretical framework for arthritis care and research for understanding disabling symptoms of older adults with RA, developing effective interventions, and assessing a full range of outcomes.

Conclusion

The initial step for RA management is to properly and effectively understand a patient's disablement process and symptom experience. Then, developing and providing the most beneficial interventions and identifying and evaluating outcomes should be pursued. In addition, factors that may affect the aforementioned process should be considered within the comprehensive realm of person, environment, and health/illness.

The DIMOA has been constructed based upon the concepts of the TSM and the DPM to serve as a theoretical framework for research and clinical practice. The TSM encompasses the ideas of the DPM, and includes more comprehensive concepts, i.e.,

dynamic interactions among domains and inter-disciplinary collaborations among patients, family caregivers, and health care providers within the context of the three nursing domains. By incorporating the DPM into the TSM, the DIMOA can help researchers understand the disabling symptom experience in individuals with RA, their management strategies, and subsequent outcomes that should not be overlooked.

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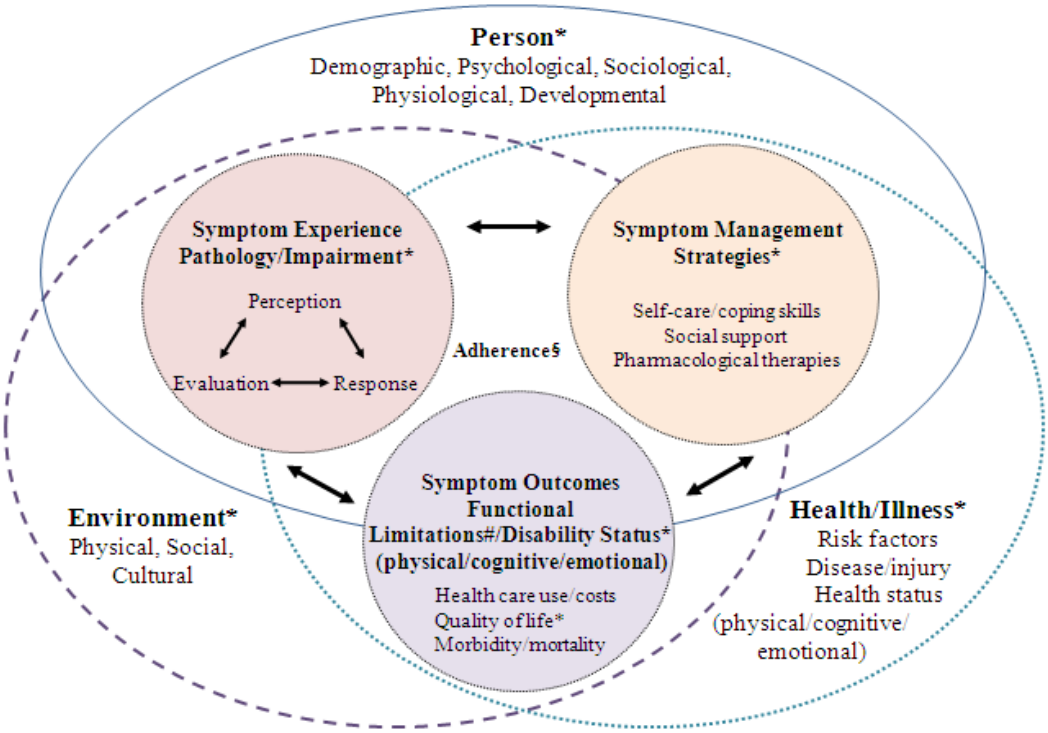

*These elements are also proposed in the DMP.

#This factor may be included in the symptom experience and/or the symptom outcome dimension depending on the disease stage or the assessment time point.

§Adherence may affect or be affected by all three dimensions.

Figure 1. Disability Intervention Model for Older Adults with Arthritis; Adapted from the Theory of Symptom Management (Humphreys, et al., 2008) and the Disablement Process Model (Verbrugge & Jette, 1994)

Chapter 4

Paper 3: Cognitive Impairment in Persons with Rheumatoid Arthritis

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Abstract

OBJECTIVE: To explore the prevalence and possible predictors of cognitive impairment in persons with rheumatoid arthritis (RA).

METHODS: Individuals from a longitudinal cohort study of RA participated in a study visit that included a range of physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices. Subjects were classified as "impaired" if they performed 1 SD below age-based population norms on at least 4 of 16 indices. Logistic regression analyses were conducted to identify which of the following were significant predictors of cognitive impairment: gender, race, income, education, depression, disease duration, disease severity, C-reactive protein (CRP), glucocorticoid use, and cardiovascular disease (CVD) risk factors.

RESULTS: 115 subjects with a mean ± SD age of 58.6 ± 10.8 years were included; 64% were female and 81% were white. The proportion of persons who were classified as cognitively impaired was 31%. Education, income, glucocorticoid use, and CVD risk factors independently predicted cognitive impairment controlling for gender, race, disease duration, disease severity, CRP, and depression. Individuals with cognitive impairment were more likely to have low education (OR = 6.18, 95% CI: 1.6-23.87), low income (OR = 7.12, 95% CI: 1.35-37.51), use oral glucocorticoids (OR = 2.92, 95% CI: 1.05-8.12), and have increased CVD risk factors (OR = 1.61, 95% CI: 1.19-2.17).

CONCLUSION: The findings of this study suggest that the burden of cognitive impairment in RA is significant, and future studies identifying specific etiological contributors to cognitive impairment are warranted.

Introduction

Studies in the general population have found cognitively impaired persons to have increased functional difficulties and reduced well-being (Bennett et al., 2002). For persons with chronic diseases such as rheumatoid arthritis (RA), intact cognitive function is critical for the successful performance of daily activities, managing and adhering to treatment regimens, and planning and initiating activities based on one's current health condition (Abeare et al., 2010). Mechanisms that have been linked to cognitive impairment in the general population, such as systemic inflammation (Gimeno, Marmot, & Singh-Manoux, 2008) and cardiovascular disease (Meyer, Rauch, Rauch, Haque, & Crawford, 2000), have particular relevance for RA. Yet, very little is known about potential factors that contribute to decreased cognitive function in persons with RA.

To date, only two studies have evaluated cognitive dysfunction in well characterized cohorts of RA patients using a comprehensive neuropsychological test battery that extends beyond bedside mental status screening exams. Bartolini et al. (2002) observed that cognitive dysfunction was common in RA patients, with prevalence rates ranging from 38% (divided/sustained attention and mental flexibility) to 71% (visuo-spatial and planning functions). In this cohort, cognitive dysfunction was also associated with neuroimaging findings, including hypoperfusion on brain single photon emission computed tomography and increased white matter alterations on magnetic resonance imaging. Additionally, Appenzeller and colleagues (2004) found cognitive impairment in 30% of the RA cohort as compared to 8% of healthy controls. These few studies have important implications in that they highlight the potential burden of cognitive impairment and its possible risk factors in persons with RA.

The purpose of this study was to explore the prevalence of cognitive impairment in a cohort of individuals with RA, and to identify the specific factors that are associated with cognitive impairment in these persons. The hypothesis was that disease-related factors would significantly affect cognitive impairment in persons with RA after controlling for sociodemographic variables.

Methods

Sample and Setting

Subjects were drawn from the University of California, San Francisco (UCSF) RA Panel, which was initiated in 1982. Details about enrollment and data collection have been described previously (Katz, Morris, & Yelin, 2006). Briefly, a random sample of rheumatologists practicing in Northern California recruited participants with RA presenting in their offices over a one month period. Eight hundred twenty two persons were enrolled between 1982 and 1983, supplemented with four additional recruitments from 1989 to 2003. Trained interviewers have conducted structured annual telephone interviews that included questions on sociodemographic characteristics, general health status, disease-related symptoms, medication use, psychological health status, physical function, and disability.

At the end of the telephone interviews in study years 2007-2009, participants who lived in the San Francisco Bay Area and were willing to travel to the UCSF were recruited for in-person assessments at the UCSF Clinical and Translational Science Institute (CTSI) Clinical Research Services (CRS) facility. In 2009, an additional 44 subjects were recruited from the UCSF rheumatology clinic and from individuals who had participated in another study of RA and had agreed to be contacted for other studies.

In total, 144 individuals participated in the CRS visits, 60% of those who were recruited and were eligible.

The CRS visits included a range of physical, psychosocial, cognitive, and biological measures. Data from the CRS visits were merged with data collected during the standardized telephone interviews. Finally, 115 subjects who had complete data on all outcomes and covariates of interest were included in this study; of participants who were excluded for the analyses, the majority were missing on family income (N=9) and neuropsychological performance (N=9), seven were missing on CVD risk factors, and six were missing on disease severity. The research protocol was approved by the UCSF Committee on Human Research, and all subjects gave their informed consent to participate.

Measures

Cognitive function

Cognitive function was assessed using a standardized neuropsychological battery that was modified from the American College of Rheumatology (ACR) neuropsychological battery (Many, 1999). This battery is primarily designed for use in a comparable rheumatic condition, systemic lupus erythematosus (SLE), and has been deemed reliable and valid (Kozora, Arciniegas, Zhang, & West, 2007; Kozora, Ellison, & West, 2004). We modified it for use in RA to minimize or control for the effects of hand-motor dysfunction.

Neuropsychological tests included the California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 1987) Learning, Short Delay, and Long Delay Recall; the Rey-Osterrieth Complex Figure Test (Rey & Osterrieth, 1993) Copy Trial, Immediate Delay,

and Long Delay Recall; the Controlled Oral Word Association Test and the Animal Naming Test (Borkowski, Benton, & Spreen, 1967); the oral version of the Symbol Digit Modalities Test (Smith, 1982); the Delis Kaplan Executive Function Scale, including Card Sorting Test (Total Correct), Design Fluency Test (Total Correct), Trail Making Test (Timing for Sequencing/Shifting Condition), and Color Word Inference Test (Delis, 2001) Inhibition and Switching Conditions; the Wechsler Adult Intelligence Scale-III Digit Span Backwards Test (Wechsler, 1997); and the short form Judgment of Line Orientation Test (Benton, 1994; Woodard et al., 1996). The duration of the neuropsychological battery was approximately 60 to 80 minutes.

Neuropsychological tests were scored to yield z-scores based on age-stratified population norms, and sixteen neuropsychological indices were derived. Using conventional cut points, subjects were classified as "impaired" if they performed 1 SD below age-stratified population norms for each cognitive test (Kozora et al., 2004; Kozora, Thompson, West, & Kotzin, 1996). A total cognitive function score was calculated by summing the number of tests on which individuals were classified as "impaired", ranging from 0 to 16 (higher scores = greater impairment). For subjects who completed at least 80% of the 16 subtests ($\geq$ 13), but did not complete one to three of the subtests, the mean z-score of the subtests that they did complete was substituted as the scores for the missing subtests before the total cognitive function score was created. Finally, persons with total cognitive function scores of four or more were classified as "cognitively impaired".

Covariates

Sociodemographics and disease characteristics (i.e., age, gender, race,

educational level, marital status, family income, presence of hypertension, use of medications including antihypertensive medicines and oral glucocorticoids, smoking status, disease duration, disease severity, and depression) were assessed based on self-reported information. Blood samples for measurement of high sensitivity C-reactive protein (CRP), total cholesterol, and high density lipoprotein cholesterol (HDL) were collected during the CRS visit and sent to a commercial laboratory for analysis. Blood pressure as well as height and weight to calculate body mass index were also measured during the study visit.

Depression was assessed using the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997; Sheehan et al., 1997), a short diagnostic structured interview corresponding to the Diagnostic and Statistical Manual (DSM)-III-R criteria for the Axis I psychiatric disorders. The MINI was administered by study clinical evaluators trained and supervised by a clinical psychologist (LJ). The MINI has been deemed reliable and valid across many populations (Lecrubier, et al., 1997; Sheehan, et al., 1997).

Severity of RA was assessed using the Rheumatoid Arthritis Disease Activity Index (RADAI) (Fransen, Langenegger, Michel, & Stucki, 2000; Stucki, Liang, Stucki, Bruhlmann, & Michel, 1995), a patient-assessed measure of disease activity in RA, covering global disease activity in the past 6 months; current joint pain, tenderness, and swelling; and current duration of morning stiffness. RADAI scores range from 0 to 10, with higher scores reflecting greater disease activity. It has been shown to be reliable and valid (Fransen, et al., 2000; Stucki, et al., 1995).

Cardiovascular disease (CVD) risk factor scores were generated based on variables in the CVD risk score profiles from the Framingham heart study (D'Agostino et

al., 2008; Pencina, D'Agostino, Larson, Massaro, & Vasan, 2009). Scores were calculated as the total number of the following CVD risk factors that were present: hypertension, systolic blood pressure > 140, antihypertensive medication use, total cholesterol > 200, HDL < 60, current smoking, and obesity (body mass index > 30). CVD risk factor scores ranged from 0 to 7, with higher scores indicating greater CVD risk.

Statistical Analyses

Chi-square analyses and t-tests were used to determine whether significant differences existed between the cognitively impaired and unimpaired groups. Logistic regression analyses were used to identify potential predictors of cognitive impairment. Variables that were significantly associated with cognitive impairment ($p < 0.05$) in bivariate regression models or had been linked with cognitive impairment in previous studies among individuals with chronic health conditions were included in multivariate regression models. Thus, in multivariate models, gender, race, education, income, duration of RA, severity of RA, depression, CRP, oral glucocorticoid use, and CVD risk factor scores were assessed as the potential predictors of cognitive impairment. The limit for significance was set at two-tailed $\alpha = 0.05$. All analyses were conducted using the IBM SPSS Statistics, version 19.0.

Results

Subject characteristics are presented in Table 1. Mean ± SD age of 115 participants was 58.6 ± 10.8 years; 64% were female and 81% were white. Sixty three percent were married/living with partners and 16% had less than 12 years of education. Mean ± SD duration of RA was 19.6 ± 11.3 years, and mean ± SD CVD risk factor score was 2.1 ± 1.7. Thirty four percent were currently treated with oral glucocorticoids, and 7%

met the criteria for major depressive disorder.

Mean ± SD total cognitive function score was 2.5 ± 2.2, and ranged from 0 to 10. The proportion of persons who were classified as cognitively impaired on each test ranged from 8% (semantic fluency test) to 29% (visuo-spatial learning/memory test). The proportion of persons classified as cognitively impaired (four or more out of 16 subtests) was 31% (Figure 1). There were no significant differences between cognitively impaired and unimpaired groups except for three variables. Cognitively impaired persons were more likely to have less than 12 years of education (p = 0.032), less than $20,000 of income ($p$ = 0.045), and more CVD risk factors (p = 0.003) than unimpaired persons.

Gender, race, education, income, depression, duration of RA, severity of RA, CRP, oral glucocorticoid use, and the number of CVD risk factors were included in multivariate logistic regression models (Table 2). These ten predictors explained 24%-34% of the variance in cognitive impairment. Of the clinical variables, current oral glucocorticoid use and CVD risk factor score independently predicted cognitive impairment (X^2(df) = 31.60(10), p < .005); education and income were the only demographic factors associated with cognitive impairment (outcome was already adjusted for age). Individuals with cognitive impairment were more likely to report current use of oral glucocorticoids (OR = 2.92, 95% CI: 1.05-8.12), and have a greater number of CVD risk factors (OR = 1.61, 95% CI: 1.19-2.17 per risk factor), controlling for all other variables in the model. Low education (OR = 6.18, 95% CI: 1.60-23.87) and low income (OR = 7.12, 95% CI: 1.35-37.51) were also significantly associated with cognitive impairment, whereas gender, race, disease duration, disease severity, CRP, and depression were not significant predictors of cognitive impairment in this cohort.

Discussion

In this study, we sought to explore the prevalence and clinical predictors of cognitive impairment in persons with RA. The proportion of persons who were classified as cognitively impaired on each test ranged from 8% to 29%. About one-third of subjects were classified as cognitively impaired on four or more tests. In multivariate models, adjusting for relevant sociodemographics, only oral glucocorticoid use and cumulative number of CVD risk factors emerged as the clinical factors independently associated with the presence of cognitive impairment.

Over 20% of subjects were found to be cognitively impaired in domains evaluating executive function (28% on the Design Fluency Test and 21% on the Trail Making Test). In addition, 29% and 18% of subjects were classified as cognitively impaired in domains evaluating visuo-spatial learning/memory and verbal learning/memory, respectively. These results are analogous to previous studies. For example, Appenzeller and colleagues (2004) found cognitive impairment in 30% of the RA cohort, with worse outcomes in domains evaluating verbal fluency and episodic memory. We found slightly lower prevalence rates in comparison to another study by Bartolini et al. (2002), who observed cognitive dysfunction in 38-71% of their cohort of RA patients. Although direct comparisons among studies may not be possible due to different classifications of cognitive impairment and diverse assessment methods used, these results do imply the significance of cognitive problems in RA. Further studies are needed that assess cognitive function in RA with standardized criteria and methodologies.

The findings of oral glucocorticoid use and CVD risk factors emerged as significant predictors of cognitive impairment in RA patients seem to be notable. In this

study, most subjects were taking relatively low-dose glucocorticoids; mean ± SD daily glucocorticoid dose was 2.1 ± 4.7-mg, and only 14 individuals were taking more than 5-mg of glucocorticoids per day. Nevertheless, subjects with any oral glucocorticoid use were about three times more likely to be cognitively impaired than those without oral glucocorticoid use. This finding is consistent with previous research. Excessive circulatory levels of corticosteroids were observed to be associated with cognitive impairment in various disease states (Belanoff, Gross, Yager, & Schatzberg, 2001). Wolkowitz and colleagues (1990) found that even single dose (1-mg dose of dexamethasone) or short-term use of corticosteroids (80-mg dose of prednisone for 5 days) were significantly related to memory problems, and raised the possible adverse effect of corticosteroids on cognitive function. This result implies that even patients with relatively low-dose glucocorticoid use may be at risk for cognitive problems.

Subjects with a greater number of CVD risk factors were more likely to be cognitively impaired in this study. Cardiovascular-related risk factors are known predictors of cognitive decline (Knopman et al., 2001; Meyer, et al., 2000; Singh-Manoux et al., 2008), and executive function may be particularly vulnerable to the effect of CVD (Chui, 2001). RA patients are more likely to have cardiovascular-related morbidity/mortality compared to non-RA patients (Maradit Kremers et al., 2005; Roifman, Beck, Anderson, Eisenberg, & Genest, 2011). Therefore, comorbid CVD risk factors including hypertension, hyperlipidemia, obesity, or current smoking may increase the prevalence of cognitive impairment in RA. In addition, the influence of glucocorticoid use and CVD may be interconnected, with some studies suggesting that glucocorticoid use may also confer a direct risk for CVD in rheumatic disease

(Mazzantini et al., 2010; Panoulas et al., 2008). Previous research has reported that RA patients with long-term low- or middle-dose glucocorticoid use had a higher prevalence of some aspects of CVD risk and incidence including hypertension and myocardial infarction than those with no glucocorticoid use (Mazzantini, et al., 2010; Panoulas, et al., 2008). Mazzantini et al. (2010) found that medium-dose long-term steroid users had a higher prevalence of hypertension compared to no or limited steroid users. Additionally, Davis et al. (2007) found that rheumatoid factor-positive patients with RA had an increased risk of CVD events after using glucocorticoids. The increased risk of cardiovascular conditions may interact with long-term glucocorticoid use to influence cognitive function. Patients with RA may be cognitively impaired not by the direct impact of disease process or symptoms such as duration, severity, or inflammation, but by the indirect impact of comorbid CVD risk factors, or even low-dose glucocorticoid use, a common regimen of RA management.

A few factors that are related to RA activity or severity have been shown to be also associated with cognitive dysfunction in previous studies. Inflammatory markers such as CRP or interleukin-6 (IL-6) are observed to be associated with incident cognitive impairment and cognitive decline in the general population (Gimeno, et al., 2008; Yaffe et al., 2003) and in other rheumatic conditions including SLE (Shucard, Gaines, Ambrus, & Shucard, 2007). Disease symptoms, such as chronic pain and psychological distress, have been linked to cognitive impairment (Hart, Wade, & Martelli, 2003). However, these factors did not emerge as significant predictors of cognitive impairment in this study. Depression is commonly observed as a risk factor for cognitive decline in other populations (Chodosh, Kado, Seeman, & Karlamangla, 2007), but did not emerge as a

significant predictor in this study, perhaps due to the relatively low prevalence of major depressive disorder in this cohort or perhaps due to the use of a dichotomous diagnostic assessment of depression in lieu of a severity scale of depressive symptomatology. More studies are needed to identify the exact contributions of these factors to cognitive dysfunction in RA patients.

This study has some limitations that should be mentioned. The sample for this study may not be representative of all patients with RA for several reasons. Many subjects were participants of a long-term prospective study of RA (active since 1983) and may be relatively healthy survivors who have been able to participate in long-term research studies. Only persons who lived in the San Francisco Bay Area and were able to travel to the UCSF clinical research center were included in the study, perhaps also biasing the sample toward more healthy individuals. Subjects were primarily white with relatively high education and income, which might limit the generalization of the study findings to certain groups.

Individuals who are cognitively impaired may be inaccurate reporters of RA disease symptoms. Information on long-term or cumulative glucocorticoid use was not available for this cohort, but would have provided added information regarding the role of glucocorticoids and cognitive impairment in RA. This was a cross-sectional study, and thus cannot provide causal information among the variables. In spite of statistically significant findings regarding the relationship between the variables of interest, the causal pathway to cognitive impairment could not be determined in this cross-sectional study. A longitudinal study design is required to identify the causal relationship between the variables of interest.

In spite of some limitations, this study has strengths and important implications. This is one of few studies that assessed a wide spectrum of cognitive domains in RA patients using a range of neuropsychological tests. We observed that a substantial subset of our participants met criteria for cognitive impairment in a range of cognitive domains including visuo-spatial functioning and executive functioning. Individuals with impairments in these domains may have difficulties in performing daily activities and maintaining self-management regimens. Additionally, many interventions for RA often require changes in knowledge, behavior, and life-style, which likely require intact functioning in these domains. In particular, poor executive function may aggravate poor physical, psychological, and social health in persons with RA (Abeare et al., 2010). This study provides support for the use of a comprehensive cognitive evaluation beyond traditional bedside screening measures as they may be insufficient and inappropriate in assessing this complex cognitive subdomain.

This study has significant implications for clinical practice. As mentioned previously, intact cognitive function in patients with chronic diseases is important for performing fundamental daily activities and managing complex health conditions such as RA. Identifying factors that affect cognitive impairment in persons with RA is an initial step for developing effective and targeted interventions that minimize its adverse outcomes. The findings of this study enhance our understanding of cognitive impairment in RA and will help lay the foundation for designing targeted interventions to prevent and improve cognitive function in these persons. Additionally, persons with RA and cognitive impairment may benefit from interventions modified for cognitively impaired patients or designed to improve cognitive function.

The results of this study emphasize the burden of cognitive impairment in RA and the importance of cognitive function assessment in clinical settings as a significant factor in RA management. Health care providers should cautiously assess cognitive status of RA patients, especially those with oral glucocorticoid use and with CVD risk factors. Substantial attention in recent years has been paid to the burden of CVD in RA. It is well known in the general population that CVD conveys risk for the development of cognitive dysfunction and management and prevention of CVD may improve cognitive function or delay the onset of cognitive decline. To date, this is the first study to evaluate the role of CVD risk in relation to cognitive function in RA. Future studies investigating both the role of CVD in precipitating cognitive alterations and the treatment and prevention of CVD in alleviating these neuropsychiatric manifestations are warranted.

In conclusion, intact cognitive function is critical for maintaining functional independence and well-being in persons with chronic diseases. Almost one-third of RA patients were found be to cognitively impaired in this study. Persons with less education, less income, oral glucocorticoid use, and increased CVD risk factors were more likely to be cognitively impaired. The findings of this study suggest that the burden of cognitive impairment in RA is significant, and future studies identifying specific etiological contributors to cognitive impairment are warranted.

Acknowledgements

We gratefully acknowledge funding support from the following sources: NIH/NIAMS Grant P60 AR053308 and NIH/NCRR UCSF-CTSI Grant UL1 RR024131.

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Table 1. Characteristics of Subjects (N = 115)

	Total (N = 115) Mean ± SD (Range) or N (%)	**Impaired (N = 41)** Mean ± SD (Range) or N (%)	**Unimpaired (N = 94)** Mean ± SD (Range) or N (%)	***p*-value**
Age (years)	58.6 ± 10.8 (25-87)	59.5 ± 11.2 (31-82)	58.2 ± 10.6 (25-87)	.544
Female	73 (63.5)	22 (61.1)	51 (64.6)	.883
White	93 (80.9)	25 (69.4)	68 (86.1)	.065
Education <12 years	97 (84.3)	26 (72.2)	71 (89.9)	**.032***
Married/with partner	72 (62.6)	20 (55.6)	52 (65.8)	.350
CVD risk factors	2.1 ± 1.7 (0-6)	2.7 ± 1.5 (0-6)	1.8 ± 1.7 (0-6)	**.003***
Income <$20,000	9 (7.8)	6 (16.7)	3 (3.8)	**.045***
Oral steroids use	39 (33.9)	15 (41.7)	24 (30.4)	.330
Duration of RA (years)	19.6 ± 11.3 (0-56)	17.6 ± 9.3 (4-37)	20.6 ± 12.1 (0-56)	.202
Severity of RA	2.4 ± 1.6 (0-6.7)	2.6 ± 1.8 (0-6.1)	2.2 ± 1.5 (0-6.7)	.291
C-reactive protein (>3)	41 (35.7)	15 (41.7)	26 (32.9)	.484
Depression	8 (7.0)	5 (13.9)	3 (3.8)	.115

Table 2. Logistic Regression Analysis: Predictors of Cognitive Impairment

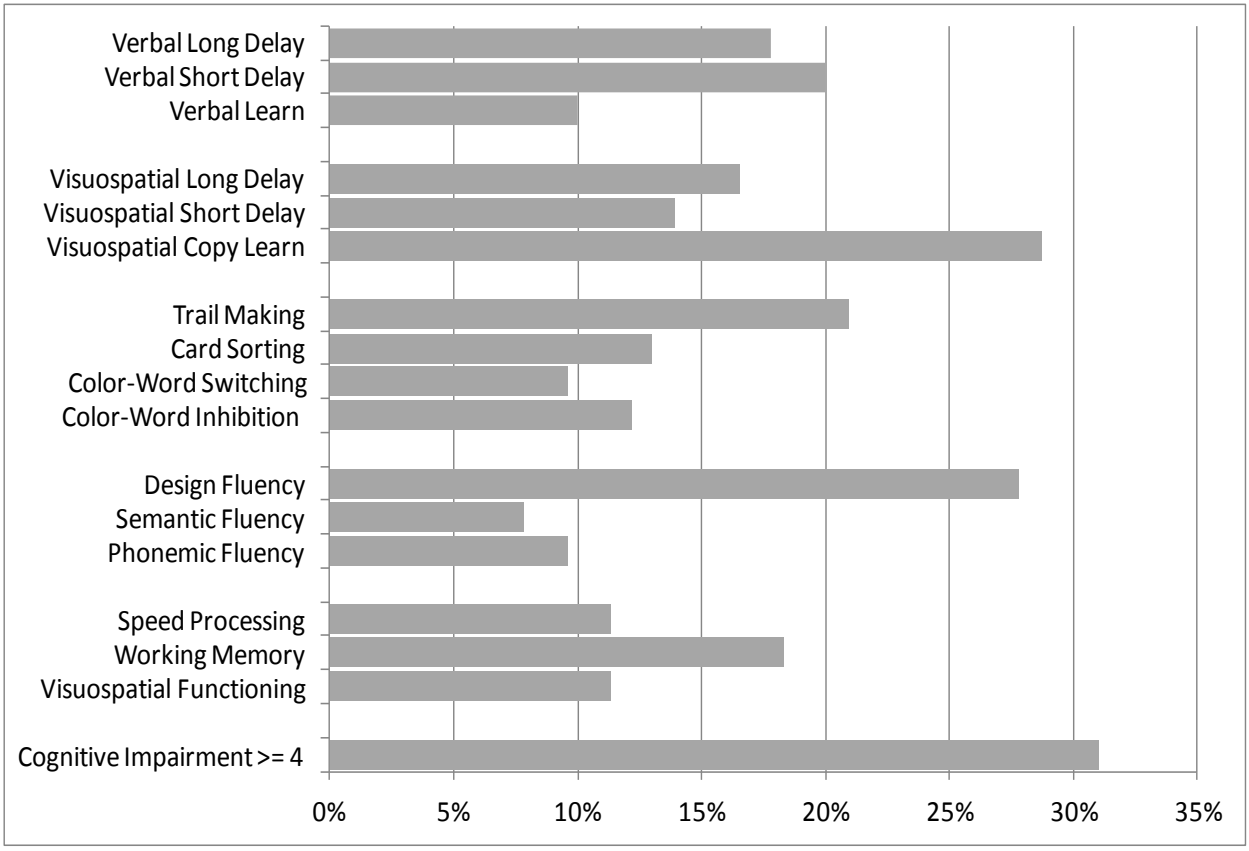
	OR (95% CI)	
Predictors	**Bivariate**	**Multivariate**
Female (male vs. female)	OR = 0.86 (0.38-1.95)	OR = 1.30 (0.48-3.55)
Race (white vs. nonwhite)	**OR = 2.72 (1.05-7.06)***	OR = 3.00 (0.85-10.56)
Education (>12 vs. <12)	**OR = 3.41 (1.22-9.59)***	**OR = 6.18 (1.60-23.87)***
Income (> 20k vs. < 20k)	**OR = 5.07 (1.19-21.58)***	**OR = 7.12 (1.35-37.51)***
Depression	OR = 4.09 (0.92-18.15)	OR = 2.65 (0.44-16.17)
Severity of RA	OR = 1.15 (0.90-1.47)	OR = 0.83 (0.59-1.16)
Duration of RA	OR = 0.98 (0.94-1.01)	OR = 0.96 (0.92-1.01)
C-reactive protein (<3 vs. >3)	OR = 1.46 (0.65-3.28)	OR = 1.21 (0.43-3.38)
Oral steroid use	OR = 1.64 (0.72-3.71)	**OR = 2.92 (1.05-8.12)***
CVD risk factor score	**OR = 1.39 (1.08-1.77)***	**OR = 1.61 (1.19-2.17)***

OR = Odds ratio; CI: Confidence interval

CVD risk factor score: Hypertension, HBP meds, systolic BP, total cholesterol, HDL, obesity, and smoking status

*Significant at $p < .0.05$

Figure 1. Characteristics of Neuropsychological Test Performance (% Impaired)



Chapter 5

Paper 4: The Relationship between Cognitive Function and Physical Function in Persons with Rheumatoid Arthritis

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Abstract

OBJECTIVE: This study examined the relationship of cognitive impairment with functional limitations and disability in persons with rheumatoid arthritis (RA).

METHODS: Individuals from a longitudinal cohort study of RA participated in study visits that included physical, psychosocial, and biological metrics. Cognitive function was assessed using a battery of 12 standardized neuropsychological measures yielding 16 indices covering a range of cognitive domains. On each test, subjects were classified as "impaired" if they performed 1 SD below age-based population norms. Total cognitive function scores were calculated by summing the transformed scores (range 0-16; higher scores = greater impairment). Functional limitations were assessed with the Short Physical Performance Battery (SPPB) and the Health Assessment Questionnaire (HAQ). Disability was measured with the Valued Life Activities (VLA) scale. Multiple regression analyses, controlling for gender, race, education, marital status, income, disease duration, disease severity, C-reactive protein, and depression were conducted to identify whether cognitive impairment was independently associated with physical function difficulties.

RESULTS: 118 subjects with mean ± SD age of 58.7 ± 10.7 years were included; 64% were female and 82% were white. In multivariate regression models, total cognitive function score was significantly associated with greater functional limitations (SPPB: β = -.27, p = .008; HAQ: β = .27, p = .001) but not with disability (VLA: β = .12, p = .120).

CONCLUSION: Cognitive impairment was significantly associated with greater functional limitations in RA patients suggesting that consideration of cognitive impairment may be warranted to improve functional status in persons with RA.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that is characterized by pain, joint stiffness/swelling, and subsequent functional limitations and disability (Dunlop et al., 2005). The proportion of persons living with RA-attributable adverse outcomes, such as functional limitations and disability, has increased over time due to longevity and disease chronicity (Hootman & Helmick, 2006). Understanding the risk factors that aggravate functional status is essential for developing effective interventions to minimize these outcomes.

For persons with chronic diseases such as RA, intact cognitive function is crucial for performing daily activities and maintaining disease management skills, including adhering to medication regimens, planning and initiating activities based on one's current condition, changing plans if pain unexpectedly worsens, and limiting behaviors that worsen pain or health status (Abeare et al., 2010). Although several mechanisms may influence cognitive function in persons with RA, cognitive function has not been extensively studied in these patients (Appenzeller, Bertolo, & Costallat, 2004).

Only two studies have evaluated cognitive function in well characterized cohorts of RA patients using a comprehensive neuropsychological test battery that extends beyond general mental status screening exams, such as the Mini-Mental State Examination (MMSE). In one study by Bartolini et al. (2002), cognitive dysfunction was observed to be common in RA patients with prevalence rates ranging from 38% (attention and mental flexibility) to 71% (visuo-spatial and planning functions). In this cohort, cognitive dysfunction was also associated with neuroimaging findings, including hypoperfusion on brain single photon emission computed tomography and increased

white matter alterations on magnetic resonance imaging. Additionally, Appenzeller and colleagues (2004) observed cognitive impairment in 30% of the RA cohort as compared to 8% of healthy controls. RA patients had significantly worse outcomes in verbal fluency and episodic memory. These few studies have important implications in that they highlight the potential burden of cognitive impairment and its possible risk factors in RA patients.

A number of studies have assessed cognitive dysfunction as one of many predictors that might exacerbate functional limitations or disability in large samples of community-dwelling individuals with various chronic health conditions (Auyeung et al., 2008; Dunlop et al., 2005; Raji et al., 2005). However, no study has examined the relationship between cognitive function and physical function in persons with RA. Therefore, the purpose of this study was to explore the relationship between cognitive function and physical function in persons with RA. The hypothesis was that cognitive impairment would be independently related to higher levels of physical function difficulties (functional limitations and disability) in persons with RA after controlling for sociodemographic and disease-related factors.

Methods

Sample and Setting

Subjects were drawn from the University of California, San Francisco (UCSF) RA Panel, which was initiated in 1982. Details about enrollment and data collection have been described previously (Katz, Morris, & Yelin, 2006). Briefly, a random sample of rheumatologists practicing in Northern California recruited participants with RA presenting in their offices over a one month period. Eight hundred twenty two persons

were enrolled between 1982 and 1983, supplemented with four additional recruitments from 1989 to 2003. Trained interviewers have conducted structured annual telephone interviews that included questions on sociodemographic characteristics, general health status, disease-related symptoms, medication use, psychological health status, physical function, and disability.

At the end of the telephone interviews in study years 2007-2009, participants who lived in the San Francisco Bay Area and were willing to travel to the UCSF were recruited for in-person assessments at the UCSF Clinical and Translational Science Institute (CTSI) Clinical Research Services (CRS) facility. In 2009, an additional 44 subjects were recruited from the UCSF rheumatology clinic and from individuals who had participated in another study of RA and had agreed to be contacted for other studies. In total, 144 individuals participated in the CRS visits, 60% of those who were recruited and were eligible.

The CRS visits included a range of physical, psychosocial, cognitive, and biological measures. Data from the CRS visits were merged with data collected during the standardized telephone interviews. Finally, 118 subjects who had complete data on all outcomes and covariates of interest were included in this study; of participants who were excluded for the analyses, the majority were missing on family income (N = 9) and neuropsychological performance (N = 9), and six were missing on disease severity. The research protocol was approved by the UCSF Committee on Human Research, and all subjects gave their informed consent to participate.

Measures

Functional limitations

The Short Physical Performance Battery **(**SPPB) (Guralnik et al., 1994) was used as an objective measure of functional limitations. The SPPB has been utilized as a reliable and valid performance-based measure of physical function in many disability studies (Gill, Murphy, Barry, & Allore, 2009; Vasunilashorn et al., 2009; Wennie Huang, Perera, VanSwearingen, & Studenski, 2010). It includes standing balance, 4-meter gait speed, and chair rising tasks. The sum of the three test scores provides a summary performance score, ranging from 0 to 12 (lower scores = greater functional limitations) (Guralnik, Ferrucci, Simonsick, Salive, & Wallce, 1995; Guralnik et al., 1994).

The Health Assessment Questionnaire (HAQ) (Fries, Spitz, Kraines, & Holman, 1980) one of the most widely used outcome measures in RA research, was used as a subjective measure of functional limitations. The HAQ includes 20 items covering 8 domains: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping, and outdoor activities. HAQ scores range from 0 to 3 with higher scores reflecting greater functional limitations (Fries, Spitz, & Young, 1982; McDowell, 2006).

Disability

The Valued Life Activities (VLA) scale (Katz & Yelin, 1994; Yelin, Lubeck, Holman, & Epstein, 1987) was administered to assess self-reported disability in daily activities. The 33-item VLA scale assesses a wide range of activities, ranging from obligatory activities (e.g., self-care) to discretionary activities (e.g., recreation and social participation). Activities that are not applicable to a subject (e.g., "taking care of children" if the subject has no children) or are not important to the subject (e.g., "household maintenance" if the spouse does all the household maintenance work) are not included in scoring the scale. Difficulty is rated on the same scale as the HAQ (0-3, higher scores =

greater disability). The VLA was scored as the mean difficulty for all rated items.

Cognitive function

Cognitive function was assessed using a standardized neuropsychological battery that was modified from the American College of Rheumatology (ACR) neuropsychological battery (Many, 1999). It is primarily recommended for systemic lupus erythematosus (SLE), and has been deemed reliable and valid (Kozora, Arciniegas, Zhang, & West, 2007; Kozora, Ellison, & West, 2004). We modified it for use in RA to minimize or control for the effects of hand-motor dysfunction.

Neuropsychological tests included the California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 1987) Learning, Short Delay, and Long Delay Recall; the Rey-Osterrieth Complex Figure Test (Rey & Osterrieth, 1993) Copy Trial, Immediate Delay, and Long Delay Recall; the Controlled Oral Word Association Test and the Animal Naming Test (Borkowski, Benton, & Spreen, 1967); the oral version of the Symbol Digit Modalities Test (Smith, 1982); the Delis Kaplan Executive Function Scale, including Card Sorting Test (Total Correct), Design Fluency Test (Total Correct), Trail Making Test (Timing for Sequencing/Shifting Condition), and Color Word Inference Test (Delis, 2001) Inhibition and Switching Conditions; the Wechsler Adult Intelligence Scale-III Digit Span Backwards Test (Wechsler, 1997); and the short form Judgment of Line Orientation Test (Benton, 1994; Woodard et al., 1996). The duration of the neuropsychological battery was approximately 60 to 80 minutes.

Neuropsychological tests were scored to yield z-scores based on age-stratified population norms, and sixteen neuropsychological indices were derived. Using conventional cut points, subjects were classified as “impaired” if they performed 1 SD

below age-stratified population norms for each cognitive index (Kozora et al., 2004; Kozora, Thompson, West, & Kotzin, 1996). A total cognitive function score was calculated by summing the number of tests on which individuals were classified as "impaired", ranging from 0 to 16 (higher scores = greater impairment). For subjects who completed at least 80% of the 16 subtests (≥ 13), but did not complete one to three of the subtests, the mean z-score of the subtests that they did complete was substituted as the scores for the missing subtests before the total cognitive function score was created.

Covariates

Self-reported information on sociodemographics and disease characteristics were assessed as covariates. Blood samples for measurement of high sensitivity C-reactive protein (CRP) were collected during the CRS visit and sent to a commercial laboratory for analysis. Depression was assessed using the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997; Sheehan et al., 1997), a short diagnostic structured interview corresponding to the Diagnostic and Statistical Manual (DSM)-III-R criteria for the Axis I psychiatric disorders. The MINI was administered by study clinical evaluators trained and supervised by a clinical psychologist (LJ). The MINI has been deemed reliable and valid across many populations (Lecrubier, et al., 1997; Sheehan, et al., 1997).

Severity of RA was assessed using the Rheumatoid Arthritis Disease Activity Index (RADAI) (Fransen, Langenegger, Michel, & Stucki, 2000; Stucki, Liang, Stucki, Bruhlmann, & Michel, 1995), a patient-assessed measure of RA disease activity, covering global disease activity in the past 6 months; current joint pain, tenderness, and swelling; and current duration of morning stiffness. RADAI scores range from 0 to 10, with higher

scores reflecting greater disease activity. It has been shown to be reliable and valid (Fransen, et al., 2000; Stucki, et al., 1995).

Statistical Analyses

Multiple linear regression analyses were used to identify the relationship between total cognitive function score and three physical function test scores, controlling for covariates (gender, race, educational level, marital status, income, disease duration, disease severity, CRP, and depression). Three separate multiple regression analyses were conducted (one for each dependent variable) to examine the independent contribution of cognitive impairment to physical function difficulties, controlling for other covariates. The limit for significance was set at two-tailed $\alpha = .05$. All analyses were conducted using the IBM SPSS Statistics, version 19.0.

Results

Subject characteristics are presented in Table 1. Mean ± SD age of 118 subjects was 58.7 ± 10.7 years. Sixty four percent were female, 82% were white, and 63% were married/living with partners. Seven percent met the criteria for major depressive disorder. Mean ± SD educational level was 15.3 ± 2.2 years and disease duration was 19.9 ± 11.2 years. Mean ± SD scores of the SPPB, HAQ, and the VLA difficulty were 9.4 ± 2.4, 0.9 ± 0.7, and 0.6 ± 0.5, respectively.

Mean ± SD total cognitive function score was 2.5 ± 2.2, and ranged from 0 to 10 (Table 2). The proportion of persons who were classified as cognitively impaired on each test ranged from 9% (semantic fluency test) to 29% (design fluency test). The proportion of persons cognitively impaired on four or more tests was 31%.

In bivariate regression models, total cognitive function score was significantly

associated with all three physical function measures (SPPB: β = -.26, p = 0.004; HAQ: β = .36, p < 0.001; VLA: β = .26, p = 0.004) (Table 3). All three multivariate regression models were statistically significant and accounted for 19-49% of the variance in physical function measures (Table 3). Total cognitive function score was significantly associated with greater functional limitations on both performance-based and self-reported tests (SPPB: β = -.27, p = 0.008; HAQ: β = .27, p = 0.001) controlling for gender, race, educational level, marital status, income, duration of RA, severity of RA, CRP, and depression. Adding total cognitive function score to the regression models significantly increased the model R^2 in both cases (p < 0.05), and was a significant factor affecting function limitations. However, total cognitive function score was not significantly associated with greater self-reported disability (VLA: β = .12, p = 0.120) controlling for all other variables in the model. Among disease-related factors, longer duration of RA was significantly associated with all three physical function measures (SPPB: β = -.22, p = 0.016; HAQ: β = .33, p < 0.001; VLA: β = .23, p = 0.002). Greater severity of RA was significantly associated with worse physical function measured by the HAQ (β = .33, p < 0.001) and the VLA (β = .49, p < 0.001). Depression was found to be significantly associated with greater VLA disability only (β = .16, p = 0.034).

Discussion

In this study, we sought to identify the relationship between cognitive impairment and physical function difficulties (functional limitations and disability) in persons with RA. In bivariate regression models, total cognitive function score was significantly associated with all three physical function measures. In multivariate regression models, after controlling for covariates, cognitive impairment was

significantly associated with greater functional limitations on both performance-based and self-reported tests, but not with greater self-reported disability.

The hypotheses of this study were largely supported. Decreased cognitive function was found to be significantly associated with increased functional limitations. These results are consistent with previous studies in the general population with or without various health conditions. For example, Greiner et al. (1996) found that cognitive function was significantly associated with physical function assessed with both performance-based and self-reported measures. Wang et al. (2002) also found a significant relationship between cognitive function and both performance-based and self-reported functional limitations in older adults.

Cognitive function was not significantly associated with our self-reported measure of disability in VLA after controlling for covariates. This finding suggests that other factors, such as psychological symptoms, may be more influential in determining VLA disability. In fact, in our analyses, depression was found to be significantly associated with disability only, but not with functional limitations. Many previous studies that found depression as a leading cause of disability and poor health outcomes support this explanation. For example, Mella et al. (2010) found that over 50% of RA patients had depressive symptoms and depressed subjects had greater disability. Morris and colleagues (2011) found that long-term patterns of depression, both intermittent and chronic, had significant adverse impact on disability and perceived health status in RA even after controlling for demographics, disease-related factors, and physical limitations.

Nearly one-third of subjects in this study were classified as cognitively impaired on four or more out of 16 subtests. About 20-30% of subjects were found to be

cognitively impaired in domains evaluating executive function; specifically 29% in the nonverbal fluency test and 21% in the sequencing and set shifting test. Similarly, 20% and 28% of subjects were classified as cognitively impaired in domains evaluating verbal learning/memory and visuo-spatial learning/memory, respectively. These results are analogous to previous studies. For example, Appenzeller and colleagues (2004) found cognitive impairment in 30% of their well characterized RA cohort. We found slightly lower prevalence rates in comparison to another study by Bartolini et al. (2002), who observed cognitive dysfunction in 38-71% of their cohort of RA patients. Although direct comparisons among studies may not be made due to the different classifications of cognitive impairment and diverse assessment methods used, our results coupled with these previous studies imply the significance of cognitive problems in RA. Further studies are needed to assess cognitive function with standardized criteria and methodologies in RA patients.

Several mechanisms have been hypothesized to influence cognitive function in persons with RA, including the systemic inflammatory process, chronic pain, psychological distress, and long-term glucocorticoid use (Appenzeller et al., 2004). Regardless of the source, the findings of this study suggest that cognitive impairment should be considered in clinical settings as a significant factor that may affect functional status among persons with RA and may place them at risk for disability. Prevention strategies to avoid further functional decline could be targeted toward these individuals.

This study is not without limitations. The sample for this study may not be representative of all patients with RA for several reasons. Many subjects were participants of a long-term prospective study of RA (active since 1983) and may be

relatively healthy survivors who have been able to participate in long-term research studies. Only persons who lived in the San Francisco Bay Area who were able to travel to the UCSF clinical research center were included in the study, perhaps also biasing the sample toward more healthy individuals. Subjects were primarily white with relatively high education and income, which might limit the generalization of the study findings to certain groups. Individuals who are cognitively impaired may be inaccurate reporters of their functioning. However, our use of a performance-based measure served to at least partially mitigate this limitation. A cross-sectional study cannot provide causal information about the variables. In spite of statistically significant findings regarding the relationship between the two variables of interest, whether cognitive impairment caused physical function difficulties or vice versa could not be determined in this cross-sectional study. A longitudinal study design is required to identify the causal relationship between the independent and dependent variables.

In spite of some limitations, this study has several strengths. Cognitive function was assessed using a standardized neuropsychological battery covering a wide spectrum of cognitive domains that provided richer information as compared to bedside mental status screening tests. To our knowledge, this is the first study that has identified the relationship between cognitive function and physical function in persons with RA. Using both subjective and objective measures, this study provided unique and comprehensive information about physical function difficulties in daily life and minimized potential bias that could be produced by use of self-report measures only.

This study has significant implications for clinical practice. Intact cognitive function in patients with chronic diseases is important for performing fundamental daily

activities and managing complex health conditions such as RA. Identifying factors that exacerbate or enhance physical function is an initial step in health management and may support the continued development of effective interventions for patients. The results of this study emphasize the burden of cognitive impairment in RA patients and the importance of cognitive function assessment in clinical settings as a significant risk factor of functional decline. Persons with RA may benefit from interventions modified for cognitively impaired patients or designed to improve cognitive function to enhance physical function and eventually promote quality of life.

Conclusion

Many population-based studies have found that individuals with low cognitive function have less ability to perform physical function tests and more disability in various aspects of daily activities. However, no study has specifically examined the relationship between cognitive function and physical function in persons with RA.

We found that cognitive impairment was relatively common in this sample and was significantly associated with increased functional limitations in persons with RA. The findings of this study suggest that consideration of cognitive impairment is warranted to improve functional status in persons with RA. Future studies may be needed to assess the impact of cognitive impairment on subsequent physical function difficulties over time with a more representative sample, and to examine the effect of interventions that consider a patient's cognitive function in efforts to improve physical function and quality of life.

Acknowledgements

We gratefully acknowledge funding support from the following sources: NIH/NIAMS

Grant P60 AR053308 and NIH/NCRR UCSF-CTSI Grant UL1 RR024131.

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Table 1. Characteristics of Subjects (N = 118)

	N (%)	Mean ± SD (Range)
Sociodemographic		
Age (years)		58.7 ± 10.7 (25-87)
Female	75 (63.6)	
White	97 (82.2)	
Educational level (years)		15.3 ± 2.2 (10-20)
Married/living with partner	74 (62.7)	
Family income		
Below $20,000	10 (8.5)	
$20,000-$40,000	20 (16.9)	
$40,000-$60,000	15 (12.7)	
$60,000-$80,000	12 (10.2)	
$80,000-$100,000	22 (18.6)	
Above $100,000	39 (33.1)	
Disease-related		
Duration of RA (years)		19.9 ± 11.2 (0-56)
RADAI score (severity of RA)		2.3 ± 1.6 (0-6.7)
High-sensitivity C-reactive protein		4.3 ± 6.6 (0.2-45.7)
Depression	8 (6.8)	
Physical Function		
Valued Life Activity Difficulty		0.57 ± 0.46 (0-2.2)
Health Assessment Questionnaire		0.93 ± 0.66 (0-2.4)
Short Physical Performance Battery		9.38 ± 2.41 (0-12)

Table 2. Characteristics of Neuropsychological Test Performance

	N (%)	Mean ± SD (Range)
Verbal Learning and Memory Impairment		
CVLT Learn	12 (10.2)	
CVLT Short Delay Free Recall	24 (20.3)	
CVLT Long Delay Free Recall	21 (17.8)	
Visuo-spatial Learning and Memory Impairment		
Rey-O Complex Figure Test Copy	33 (28.0)	
Rey-O Immediate Delay	16 (13.6)	
Rey-O Long Delay	18 (15.3)	
Fluency Impairment		
Controlled Oral Word Association (Phonemic Fluency)	12 (10.2)	
Animal Naming (Semantic Fluency)	10 (8.5)	
Design Fluency	34 (28.8)	
Executive Function Impairment		
Color-Word Inhibition	14 (11.9)	
Color-Word Switching	12 (10.2)	
Card Sorting	16 (13.6)	
Trail Making Condition 4	25 (21.2)	
Visuo-spatial Impairment		
Judgment of Line Orientation	13 (11.0)	
Working Memory and Speed Processing Impairment		
Symbol Digit Modalities	22 (18.6)	
Digit Span Backwards	14 (11.9)	
At least 4 of cognitive tests impaired	37 (31.4)	
Total Cognitive Function Score		2.5 ± 2.2 (0-10)

Table 3. Relationship between Total Cognitive Function Score and Physical Function Measures

	Bivariate		Multivariate*	
	Std. β	p	Std. β	p
Short Physical Performance Battery (SPPB)	**-0.26**	**0.004**	**-0.27**	**0.008**
Health Assessment Questionnaire (HAQ)	**0.36**	**< 0.001**	**0.27**	**0.001**
Valued Life Activities (VLA) Difficulty	**0.26**	**0.004**	0.12	0.12

* Covariates: Gender, race, educational level, marital status, family income, duration of RA, severity of RA, CRP, and depression.

* Note: On SPPB, lower scores reflect worse functioning; on HAQ and VLA, higher scores reflect worse functioning.

*Significant at $p < .0.05$

Chapter 6: Synthesis

The primary aim of this dissertation was to explore the relationship between cognitive function and physical function in persons with rheumatoid arthritis (RA). The hypothesis was that cognitive impairment would be independently related to higher levels of physical function difficulties (functional limitations and disability) in persons with RA after controlling for other variables (gender, educational level, marital status, family income, duration of RA, severity of RA, C-reactive protein [CRP], and depression). The secondary aim was to investigate the significant factors affecting cognitive impairment in persons with RA. The hypothesis was that disease-related factors would be significant factors affecting cognitive impairment in persons with RA after controlling for other sociodemographic variables. The aims were achieved through cross-sectional secondary data analyses of an ongoing longitudinal study. The purpose of this final section is to synthesize the results of the two analyses. First, the results will be summarized after reflecting the theoretical models that guided this research. Limitations and strengths will be discussed, followed by implications for clinical practice and suggestions for future research.

Theoretical Concepts

A Disability Intervention Model for Older Adults with Arthritis (DIMOA) has guided this dissertation. A nursing model, the Theory of Symptom Management (TSM) (Humphreys, et al., 2008), and a medical model, the Disablement Process Model (DPM) (Verbrugge & Jette, 1994), contributed to the development of the DIMOA. It is essentially based upon the TSM, but with incorporation of key elements of the

disablement process of RA, so that it can be utilized as a theoretical foundation specifically for RA management in research and clinical practice.

The symptom management model was first introduced by the symptom management faculty group at the UCSF School of Nursing in 1994 (Larson et al., 1994). After a few revisions, the TSM was proposed in 2008 as a middle range theory for nursing (Humphreys, et al., 2008). The TSM comprises three essential components, namely the symptom experience, symptom management strategies, and symptom outcomes. Dynamic relationships among these concepts are placed within a three-dimentional sphere of person, environment, and health/illness which are the main domains of nursing science.

The DPM, first proposed by Verbrugge and Jette (1994), describes: (a) how medical conditions affect functioning in particular body systems, physical and mental actions, and daily activities, and (b) how personal and environmental factors exacerbate or retard the disablement process. Four concepts, pathology, impairments, functional limitations, and disability, consist of the main pathway of the DPM. The main pathway may be affected by a variety of contextual factors, including risk factors, interventions, and exacerbators.

The two models include a wide range of concepts and other contextual variables that may affect a patient's symptom management and disease process. Both models have been utilized as guiding theoretical frameworks for research and clinical practice with diverse populations. However, both models have some limitations that need to be considered (refer to the second paper). With a comprehensive understanding of the

concepts, applications, strengths, and limitations of the two models, the DIMOA has been created.

The DIMOA includes the three interrelated concepts of symptom management (i.e., symptom experience, symptom management strategies, and symptom outcomes) that correspond to the TSM. These main concepts influence or are influenced by contextual factors that are situated within the three domains of nursing science (i.e., person, environment, and health/illness). The DIMOA accepts the bidirectional, complex, dynamic interactions among all components within the model representing the comprehensive aspects of the disablement process and its interventions in persons with RA.

The components of pathology and impairments in the DPM are placed in the symptom experience dimension. Functional limitations can be placed in the symptom experience or in the symptom outcomes dimension depending on the duration and severity of the disease or symptoms and the assessment time point. As disability encompasses the physical, cognitive, and emotional aspects of a person's health status that may affect his/her psychological well-being and quality of life, it should be assessed as one of the most important symptom outcomes.

The contextual domains of person, environment, and health/illness are depicted in the DIMOA as in the TSM, reflecting the dynamic interactions among all domains within the model. Self-care/coping skills, social support, as well as conventional pharmacological treatments are included in the DIMOA under the dimension of symptom management strategies. The adherence component is depicted in the middle of the

DIMOA, because it may affect or be affected by all three dimensions, such as symptom characteristics, desirability of the interventions, or health outcomes, as well as their interactions within the model.

In the DIMOA, global outcomes (e.g., hospitalization, institutionalization, death, happiness, life satisfaction, and well-being) which may be caused by the long-term disability experience can be explained and evaluated as symptom outcomes which include a person's various aspects of health status (physical/cognitive/emotional), quality of life, health care use/costs, and morbidity/mortality.

The DIMOA has been constructed based upon the concepts of the TSM and the DPM which address the extensive aspects of an individual's disablement process and symptom management. The TSM encompasses the ideas of the DPM, and includes more comprehensive concepts, i.e., the dynamic interactions among domains and inter-disciplinary collaborations among patients, family caregivers, and health care providers within the context of the three nursing domains. By incorporating the DPM into the TSM, the DIMOA can help researchers understand the disabling symptom experience in individuals with RA, management strategies, and subsequent outcomes that should not be overlooked.

Summary of Findings

Prevalence and Predictors of Cognitive Impairment

Mean ± SD total cognitive function score was 2.5 ± 2.2, and ranged from 0 to 10. The proportion of persons who were classified as cognitively impaired on each test ranged from 8% (semantic fluency test) to 29% (visuo-spatial learning/memory test). The

proportion of persons classified as cognitively impaired (4 or more out of 16 subtests) was 31%.

In bivariate logistic regression models, non-white race (OR = 2.72, 95% CI: 1.05-7.06), low education (OR = 3.41, 95% CI: 1.22-9.59), low income (OR = 5.07, 95% CI: 1.19-21.58), and increased cardiovascular disease (CVD) risk factors (OR = 1.39, 95% CI: 1.08-1.77 per risk factor) were significantly associated with cognitive impairment ($p < 0.05$). Gender, race, education, income, depression, duration of RA, severity of RA, CRP, oral steroid use, and CVD risk factor score were included in multivariate logistic regression models. Ten predictors explained 24%-34% of the variance in cognitive impairment. Of the clinical variables, oral steroid use and CVD risk factor score independently predicted cognitive impairment (X^2(df) = 31.60(10), $p < .005$); education and income were the only demographic factors associated with cognitive impairment (outcome was already adjusted for age). Individuals with cognitive impairment were more likely to report current use of oral steroids (OR = 2.92, 95% CI: 1.05-8.12), and have a greater number of CVD risk factors (OR = 1.61, 95% CI: 1.19-2.17 per risk factor), controlling for all other variables in the model. Low education (OR = 6.18, 95% CI: 1.60-23.87) and low income (OR = 7.12, 95% CI: 1.35-37.51) were significantly associated with cognitive impairment, whereas gender, race, disease duration, disease severity, CRP, and depression were not significant predictors of cognitive impairment in this cohort.

Relationship between Cognitive Function and Physical Function

In bivariate regression models, total cognitive function score was significantly associated with all three physical function measures (Short Physical Performance Battery

[SPPB]: β = -.26, p = 0.004; Health Assessment Questionnaire [HAQ]: β = .36, p < 0.001; Valued Life Activities [VLA]: β = .26, p = 0.004). All three multivariate regression models were statistically significant and accounted for 19-49% of the variance in physical function measures. Total cognitive function score was significantly associated with greater functional limitations on both performance-based and self-reported tests (SPPB: β = -.27, p = 0.008; HAQ: β = .27, p = 0.001) controlling for gender, race, educational level, marital status, income, duration of RA, severity of RA, CRP, and depression. Adding total cognitive function score to the regression models significantly increased the model R^2 in both cases (p < 0.05), and was a significant factor affecting function limitations. However, total cognitive function score was not significantly associated with greater self-reported disability (VLA: β = .12, p = 0.120) controlling for all other variables in the model. Among disease-related factors, duration of RA was significantly associated with all three physical function measures (SPPB: β = -.22, p = 0.016; HAQ: β = .33, p < 0.001; VLA: β = .23, p = 0.002). Severity of RA was significantly associated with the HAQ (β = .33, p < 0.001) and the VLA (β = .49, p < 0.001). Depression was found to be significantly associated with the VLA disability only (β = .16, p = 0.034).

Discussion

Prevalence and Predictors of Cognitive Impairment

In this study, I sought to explore the prevalence and clinical predictors of cognitive impairment in persons with RA. The proportion of persons who were classified as cognitively impaired on each test ranged from 8% to 29%. About one-third of subjects

were classified as cognitively impaired on four or more tests. In multivariate models, adjusting for relevant sociodemographics, only oral steroid use and cumulative number of CVD risk factors emerged as the clinical factors independently associated with the presence of cognitive impairment.

Over 20% of subjects were found to be cognitively impaired in domains evaluating executive function (28% on the Design Fluency Test and 21% on the Trail Making Test). In addition, 29% and 18% of subjects were classified as cognitively impaired in domains evaluating visuo-spatial learning/memory and verbal learning/memory, respectively. These results are analogous to previous studies. For example, Appenzeller and colleagues (2004) found cognitive impairment in 30% of the RA cohort, with worse outcomes in domains evaluating verbal fluency and episodic memory. I found slightly lower prevalence rates in comparison to another study by Bartolini et al. (2002), who observed cognitive dysfunction in 38-71% of their cohort of RA patients. Although direct comparisons among studies may not be possible due to different classifications of cognitive impairment and diverse assessment methods used, these results do imply the significance of cognitive problems in RA. Further studies are needed that assess cognitive function in RA with standardized criteria and methodologies.

The findings of oral steroid use and CVD risk factors as significant predictors of cognitive impairment in RA patients seem to be notable. In this study, most subjects were taking relatively low-dose steroids; mean ± SD steroid dose was 2.1 ± 4.7-mg, and only 14 were taking more than 5-mg of steroids. Nevertheless, subjects with oral steroid use were about three times more likely to be cognitively impaired than those without oral

steroid use. This finding is consistent with previous research. Excessive circulatory levels of corticosteroids were observed to be associated with cognitive impairment in various disease states (Belanoff, Gross, Yager, & Schatzberg, 2001). Wolkowitz and colleagues (1990) found that even single dose (1-mg dose of dexamethasone) or short-term use of corticosteroids (80-mg dose of prednisone for 5 days) were significantly related to memory problems, and raised the possible adverse effect of corticosteroids on cognitive function. This result implies that even patients with relatively low-dose of steroid use may be at risk for cognitive problems.

Subjects with a greater number of CVD risk factors were more likely to be cognitively impaired in this study. Cardiovascular-related risk factors are known predictors for cognitive decline (Knopman et al., 2001; Meyer, Rauch, Rauch, Haque, & Crawford, 2000; Singh-Manoux et al., 2008), and executive function may be particularly vulnerable to CVD (Chui, 2001). RA patients are more likely to have cardiovascular-related morbidity/mortality compared to non-RA patients (Maradit Kremers et al., 2005; Roifman, Beck, Anderson, Eisenberg, & Genest, 2011). Therefore, comorbid CVD risk factors such as hypertension, hyperlipidemia, obesity, or current smoking may increase the prevalence of cognitive impairment in RA. In addition, while the research remains inconclusive, some studies have posited that glucocorticoid use also confers a direct risk for CVD in rheumatic disease (Mazzantini et al., 2010; Panoulas et al., 2008). RA patients with long-term low- or middle-dose glucocorticoid use had a higher prevalence of some aspects of CVD risk and incidence including hypertension and myocardial infarction than those with no glucocorticoid use (Mazzantini, et al., 2010; Panoulas, et al.,

2008). Mazzantini et al. (2010) found that medium-dose long-term steroid users had a higher prevalence of hypertension compared to no or limited steroid users. Additionally, Davis III et al. (2007) found that rheumatoid factor-positive patients with RA had an increased risk of CVD events after using glucocorticoids. The increased risk of cardiovascular conditions may interact with long-term corticosteroid use to influence cognitive function. Patients with RA may be cognitively impaired not by the direct impact of disease process or symptoms such as duration, severity, or inflammation, but by the indirect impact of comorbid CVD risk factors, or even low-dose steroid use, an indispensable regimen for RA management.

A few factors that are related to RA activity or severity have been shown to be also associated with cognitive dysfunction in previous studies. Inflammatory markers such as CRP or interleukin-6 (IL-6) have been observed to be associated with incident cognitive impairment and cognitive decline in the general population (Gimeno, Marmot, & Singh-Manoux, 2008; Yaffe et al., 2003) and in persons with other rheumatic conditions including systemic lupus erythematosus (Shucard, Gaines, Ambrus, & Shucard, 2007). Disease symptoms, such as chronic pain and psychological distress, are associated with cognitive impairment (Hart, Wade, & Martelli, 2003). However, these factors were not significant predictors of cognitive impairment in this study. Depression is commonly observed as a risk factor for cognitive decline in other populations (Chodosh, Kado, Seeman, & Karlamangla, 2007), but did not emerge as a significant predictor in this study. This may have been due to the relatively low prevalence of major depressive disorder in this cohort or due to the use of a dichotomous diagnostic

assessment of depression in lieu of a severity scale of depressive symptomatology. More studies are needed to identify the exact contributions of these factors to cognitive dysfunction in RA patients.

Relationship between Cognitive Function and Physical Function

In this study, I sought to identify the relationship between cognitive impairment and physical function difficulties (functional limitations and disability) in persons with RA. In bivariate regression models, total cognitive function score was significantly associated with all three physical function measures. In multivariate regression models, after controlling for covariates, total cognitive function score was significantly associated with greater functional limitations on both performance-based and self-reported tests, but not with greater self-reported disability.

The hypotheses of this study were largely supported. Cognitive function was found to be significantly correlated with both measures of functional limitations. These results are consistent with previous studies in the general population with or without various health conditions. For example, Greiner et al. (1996) found that cognitive function was significantly associated with physical function assessed with both performance-based and self-reported measures. Wang, van Belle, Kukull, and Larson (2002) also found a significant relationship between cognitive function and both performance-based and self-reported functional limitations in older adults. Many interventions for RA often require changes in knowledge, behavior, and life-style, which may, in turn, require intact cognitive functioning. This result implies that cognitively impaired persons may have increased difficulties in performing daily activities and

maintaining self-management strategies, and thus have increased functional dependence and reduced well-being.

Total cognitive function score was not significantly associated with total mean VLA difficulty score controlling for other covariates. This finding suggests that other factors, such as psychological symptoms, may be more influential in determining VLA disability. In fact, depression was found to be significantly associated with disability only, but not with functional limitations. Many previous studies that found depression as a leading cause of disability and poor health outcomes support this explanation. For example, Mella, Bertolo, and Dalgalarrondo (2010) found that over 50% of RA patients had depressive symptoms and depressed subjects had greater disability. Morris and colleagues (2011) found that long-term patterns of depression, both intermittent and chronic, had a significant adverse impact on disability and perceived health status in patients with RA even after controlling for demographics, disease-related factors, and physical limitations.

The results of this study reflected the concepts of my study model, the DIMOA. Among significant predictors of cognitive impairment (symptom experience), income and education can be placed in the domain of person or environment. Oral steroid use and CVD risk factors can be placed in the domain of person or health/illness. Cognitive impairment (symptom experience) was associated with functional limitations (symptom outcomes) controlling for other contextual variables (Figure 1). The findings of this study show that: a) a person's symptom experience has a significant association with symptom outcomes, and b) it can influence or be influenced by the contextual domains of person,

environment, and health/illness. Although the directions between the variables cannot be determined by this cross-sectional study, the significant associations existed among the concepts and the contextual domains of the DIMOA. This is the first study utilizing the combined concepts of disablement and symptom management in persons with RA and provided the rationale for its possible applicability in arthritis care. Further studies with more representative samples are warranted to identify the dynamic relationships among these variables in persons with RA.

Limitations

This study has some limitations that should be mentioned. The sample for this study may not be representative of all patients with RA for several reasons. Many subjects were participants of a long-term prospective study of RA (active since 1983) and may be relatively healthy survivors who have been able to participate in long-term research studies. Only persons who lived in the San Francisco Bay Area and were able to travel to the UCSF CRS visit were included in the study, perhaps also biasing the sample toward more healthy individuals. Subjects were primarily white with relatively high education and income, which might limit the generalization of the study findings to certain groups.

Individuals who are cognitively impaired may be inaccurate reporters of RA disease symptoms. However, the use of a performance-based measure served to at least partially mitigate this limitation. Information on long-term or cumulative glucocorticoid use was not available for this cohort, but would have provided added information regarding the role of glucocorticoids and cognitive impairment in RA.

A cross-sectional study cannot provide causal information among the variables. In spite of statistically significant findings regarding the relationship between the variables of interest, whether cognitive impairment caused physical function difficulties or whether the predictors caused cognitive impairment could not be determined in this cross-sectional study. A longitudinal study design is required to identify the causal relationship between the variables of interest.

Strengths

In spite of some limitations, this study has several strengths. This is one of few studies that assessed a wide spectrum of cognitive domains in RA patients using a range of neuropsychological tests. A substantial subset of participants met criteria for cognitive impairment in a range of cognitive domains including visuo-spatial functioning and executive functioning. Individuals with impairments in these domains may have difficulties in performing daily activities and self-management regimens. Additionally, many interventions for RA often require changes in knowledge, behavior, and life-style, which may, in turn, require intact functioning in these domains. In particular, poor executive function may aggravate poor physical, psychological, and social health in persons with RA (Abeare et al., 2010). This study provides support for the use of a comprehensive cognitive evaluation beyond traditional bedside screening measures as they may be insufficient and inappropriate in assessing this complex cognitive subdomain. To my knowledge, this is the first study that has identified the relationship between cognitive function and physical function in RA patients. Using both subjective and objective measures provided comprehensive information about physical function

difficulties in daily life and minimized potential bias that could be produced by use of self-report measures only.

Implications

This study has significant implications for clinical practice because as mentioned above, cognitive function in patients with chronic diseases is important for performing fundamental daily activities and managing health conditions. Identifying factors that affect cognitive impairment in patients is an initial step for developing effective and targeted interventions which minimize its adverse outcomes on their functional status.

The results of this study emphasize the burden of cognitive impairment in RA and the importance of cognitive function assessment in clinical settings as a significant factor that may affect functional status among persons with RA. Health care providers should carefully assess the cognitive status of RA patients, especially those with oral steroid use and with CVD risk factors. Substantial attention in recent years has been paid to the burden of CVD in RA. It is well known in the general population that CVD conveys risk for the development of cognitive dysfunction and the prevention of CVD may improve cognitive function or delay the onset of cognitive decline. If health care providers effectively manage comorbid CVD and related risk factors in RA patients, this will have a great impact on preventing or delaying cognitive impairment in these patients. Considering the high prevalence of CVD and their various adverse outcomes in these patients, the assessment and management of CVD risk factors in primary health care settings is recommended as an important RA intervention guideline. Future studies investigating both the role of CVD in precipitating cognitive alterations and the treatment

and prevention of CVD in alleviating these neuropsychiatric manifestations patients are warranted.

The findings of this study will help lay the foundation for designing targeted interventions to improve cognitive function in these patients. Persons with RA may benefit from interventions modified for cognitively impaired patients or designed to improve cognitive function. Prevention strategies to avoid further functional decline could be targeted toward these individuals. For example, health care providers may use diverse educational methods (e.g., educational sessions/discussions with individuals, small-groups, or family caregivers) and materials (e.g., handouts, photos, or flyers) for cognitively impaired patients to enhance their understanding. Repeatable sessions and follow-ups may also help patients adhere to medication regimens and self-management strategies.

Future research

Future studies may be needed that: a) develop a standardized test battery for cognitive assessment in RA, b) assess the impact of cognitive impairment on subsequent physical function difficulties over time with a more representative sample, and c) examine the effect of interventions that consider a patient's cognitive function in efforts to improve physical function and quality of life.

In addition, assessing perceived cognitive complaints and investigating the relationship with objective neuropsychological performance is suggested. Investigating the role of psychological distress, depression or fatigue, on cognitive and physical health status in RA patients may also be an important area for future research.

Conclusion

Intact cognitive function is crucial for maintaining functional independence and well-being in persons with chronic diseases including RA. Many population-based studies have found that individuals with low cognitive function have less ability to perform physical function tests and more disability in various aspects of daily activities.

Almost one-third of RA patients were found be to cognitively impaired in this study. Persons with less education, less income, oral steroid use, and more CVD risk factors were more likely to be cognitively impaired. Cognitive impairment was significantly associated with increased functional limitations in persons with RA.

The findings of this study suggest that: a) the burden of cognitive impairment in RA is substantial, b) identifying specific etiological contributors to cognitive impairment are warranted, and c) assessing cognitive dysfunction in clinical settings is crucial for improving functional status in persons with RA.

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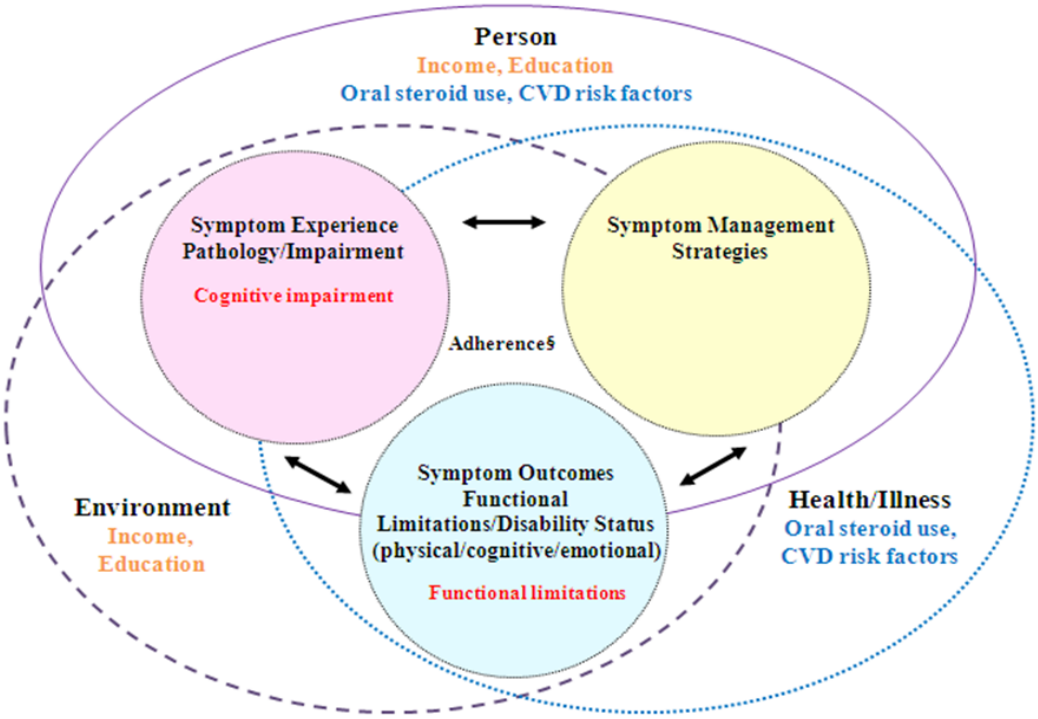

Figure 1. An Example of the Application of the DIMOA in Arthritis Research

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