THE ASSOCIATION BETWEEN PHYSICAL ACTIVITY, COGNITIVE FUNCTION, AND

PERFORMANCE OF ACTIVITIES OF DAILY LIVING IN PATIENTS WITH EARLY

ALZHEIMER'S DISEASE

BY

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Abstract

Alzheimer's disease (AD) is a common disease among the elderly. Physical activity may be beneficial for people with AD as it may slow the rate of decline in cognitive and motor abilities. This retrospective correlational study explored the association between physical activity, cognitive function, and performance of activities of daily living (ADLs) in early-stage AD. The sample consisted of 112 participants divided on 2 groups; AD and non-demented controls. Results showed that the AD group exhibited significant declines in cognition, function, and practice of physical activity over a period of 2 years compared to the control group ($p<.002$). Less practice of household activities and physical leisure activities was significantly associated with decline in the performance of ADLs ($p <.05$) in people with AD. Additionally, cognitive function significantly predicted functional decline ($p<.001$) in AD. In conclusion, physical activity may be an important part of maintaining independence in people with early AD.

Introduction

Alzheimer's disease (AD) is a chronic degenerative brain syndrome characterized by a progressive decline in cognitive functions including memory, thinking, decision-making, comprehension, calculation, language, and learning capacity (World Health Organization [WHO] 2009a). This decline is sufficient to impair personal daily life activities. It is also accompanied by psychological and behavioral symptoms including depression, agitation, aggression, psychosis, apathy, anxiety, purposeless behavior, and disorders of sleep (Chen, Borson, & Scanlan, 2000; Cummings, & Back, 1998; Forstl & Kurz, 1999).

AD is the sixth major cause of death in the United States and the most common cause of dementia, accounting for 50-70% of the cases. About 5.3 million people aged 65 years and older in the United States are living with AD, and by 2050 this number could increase up to 16 million (Alzheimer's Association [AA], 2009; American Health Assistance Foundation [AHAF], 2009). AD is also a common disease worldwide with an estimated18 million people affected, and by 2050, this figure is projected to grow to nearly 34 million (WHO, 2006).

AD is a progressive degenerative disease. Losses in regional brain structural integrity, circuitry, and neuronal processes threaten the individual's ability to express functional capacity at several levels of severity (Archer & Kostrzewa, 2009). Function is defined as the ability to complete major daily activities including activities of daily living (ADL) and more complex instrumental activities of daily living (IADL) (Yu, Kolanowski, Strumpf, & Eslinger, 2006). Examples of ADLs include dressing, eating, bathing, and functional mobility, and examples of IADLs include child rearing, communication management, community mobility, and financial management (Roley, et al., 2008). Functional decline is a major contributor to poor healthcare outcomes in people with AD. At first, decline in cognitive abilities is most evident in AD due to

neural degeneration. With the disease progress, this decline increases and affects the individual's functional ability to perform ADLs and IADLs. Consequently, individuals with AD become less independent in a wide range of occupations including ADLs, IADLs, work, and leisure (Levitt, 2007). Increased dependence in ADLs-IADLs is most significant because it severely limits the quality of life of persons with AD and often the caregivers (Rive et al., 2005).

Physical activity can be defined as any movement that requires energy expenditure and is produced by the body's skeletal muscles (WHO, 2009b). Physical activity has many benefits for individuals with dementia, AD (Heyn, Abreu, & Ottenbacher, 2004; Rolland, Abellan van Kan, & Vellas, 2008; Yu, Kolanowski, Strumpf, & Eslinger, 2006), and for older adult as well (Stewart, 2005; Vogel, et al., 2009; Warburton, Nicol, & Bredin, 2006). It was shown to have a significant and independent preventive effect on cognitive decline or dementia (Rolland, Abellan van Kan, & Vellas, 2008). Also, it is plausible that higher levels of physical activity stimulates appetite, improves bowel movement, increases energy expenditure, facilitates access to human relationships, and may result in increased food intake, less fatigue, and better sleep, mood, and quality of life and finally better cognitive functioning in individuals with AD. Heyn et al 2004 conducted a meta-analysis and concluded that exercise training improved behavior disturbances, physical function, and cognitive function in people with cognitive impairment or dementia.

In addition, the beneficial effect of physical activity on the health of older adults has been documented throughout the literature (Prohaska, et al., 2006; Stewart, 2005; Vogel, et al., 2009; Warburton, Nicol, & Bredin, 2006). Older adults engaged in regular physical activity demonstrate improved balance, strength, coordination and motor control, flexibility, and endurance (Keysor & Jette, 2001; WHO, 2009c). Physical activity also increases fitness, physical function, cognitive function, and positive behavior in this age group (Heyn, Abreu, &

Ottenbacher, 2004). In addition, physical activity reduces the incidence of many diseases and disorders. For example, type 2 diabetes and glucose intolerance (Laaksonen, et al., 2005; Van Dam, Schuit, Feskens, Seidell, & Kromhout, 2002), stroke and hip fractures (Cavill, Kahlmeier, & Racioppi 2006), and mortality rates due to cardiovascular problems or stroke (Bijnen, et al., 1998; Fraser & Shavlik, 1997; Fried, et al., 1998). The apparent beneficial influence of physical exercise on overall health, preservation of cognitive function, and maintenance of independence through support of functional performance of activities of daily living has lead to this study being developed.

AD is a serious health care problem due to the decline in memory and other cognitive functions that lead to reduced independence and has a wide-ranging impact on individuals, families, and healthcare systems. For this reason, it is crucial that researchers explore, test, and develop any possible treatment that may reduce the impact of AD on people and communities. Some of these treatments are designed to cure the disease (e.g., medications) while others are tailored to reduce the incidence and to delay the progress of the disease (e.g., medications, diet, and physical activity). It is also important that researchers understand the mechanism by which any proposed treatment works and how it affects patients with AD in different stages of the disease. The purpose of this study is to explore the association between physical activity, cognitive function, and performance of activities of daily living in a group of patients with AD. We hypothesized that the groups will have different and unequal scores on the selected measures of physical activity, cognitive function, and ADLs in this study. We anticipated that the AD group scores would be less than the non-demented group scores. We also hypothesized that higher levels of physical activity will be associated with better performance of activities of daily

living and cognitive performance in individuals with early AD. Finally, we hypothesized that cognitive function may predict better performance of ADLs.

Research Questions

This study focused on addressing the hypotheses through three research questions:

1. Are there any differences in the cognitive performance, performance of ADLs, and practice of physical activity between the AD and non-demented group at baseline and during follow up?

2. Are higher levels of physical activity associated with better performance of ADLs and cognitive performance in individuals in the early stages of AD? Is the association stronger in demented participants compared to non-demented participants?

3. Is cognitive function predictive of better performance of ADLs in individuals with early stages of AD?

 This study was designed to help health care professionals better understand the relationship between these variables and the progress of AD.

Methods

The KU Brain Aging Project is a pioneer research project directed by Dr. Jeffery Burns to promote healthy brain aging. It was designed to study the brain changes associated with aging. Thus, it will help identify specific ways to promote healthy brain aging and, perhaps, prevent the onset of Alzheimer's disease. This study utilized data collected in the Brain Aging Project between November 2004 and January 2008. 161 individuals were enrolled in the study, and were distributed on two groups: a) early stage AD group (N= 78); and b) non-demented group (N=83). The study employed an observational longitudinal design with a two-year follow-up of a cohort of individuals with early AD.

Potential participants were tracked in the greater Kansas City bi-state area (Missouri and Kansas) and nearby cities including Lawrence, Topeka, and Atchison on the Kansas side and St. Joseph, Warrensburg, and Chillicothe on the Missouri side. The recruitment plan was very efficient and included advertisements on radio, newspapers, internet as well as public lectures and printed advertisements.

All participants with early AD meeting the inclusion and exclusion criteria were enrolled, and non-demented participants meeting the inclusion and exclusion criteria were enrolled in the control group. Individuals in the non-demented group were not necessarily the caregivers of participants in the AD group. The inclusion criteria included subjects aged 65 years or older. The Clinical Dementia Rating (CDR) scale was used to determine the presence or absence of dementia as well as its severity –if present- (Morris, 1993). An available informant or caregiver who could accompany the participant to clinical evaluations and to serve as a study partner was also necessary. The exclusion criteria included: 1) diagnosis of neurological disorders other than AD that have the potential to impair cognition (e.g., Parkinson's disease, stroke); 2) diagnosis of diabetes (defined as a clinical diagnosis and the use of a anti-diabetic medication); 3) history of coronary artery disease (coronary artery bypass surgery, stent placement, history of angina or myocardial infarction); 4) pulmonary disease that may limit their exercise performance (asthma, COPD); 5) significant orthopedic issues (e.g., osteoarthritis, spinal stenosis) that may limit their ability to perform the maximal exercise test; 6) clinically significant depressive symptoms; 7) abnormalities in B12, RPR, or thyroid function that may account for the cognitive symptoms; 8) use of psychoactive and investigational medications; or 9) significant visual or auditory impairment, or systemic illness that may have prevented completion of the two-year study.

The clinical evaluation used at Washington University was modified and used for this study's clinical evaluation. A trained clinician conducted semi-structured interviews with the participant and with the study partner - a spouse or an adult child of the participant-knowledgeable about the participant. The study partner was contacted prior to the evaluation and informally interviewed by a nurse coordinator to assess their depth of knowledge and insight into the participant's daily activities. Data was collected from participants through 3-5 visits in each phase (baseline and follow-up). During each visit different instruments and procedures were applied to gather all necessary information. The Clinical Dementia Rating (CDR) scale was used to determine the presence or absence of dementia as well as its severity –if present- (Morris, 1993). A score of (0) on the CDR indicates absence of dementia, and a score of (.5) or (1) on a scale of (3) represents mild dementia.

A nurse clinician collected information about medications, past medical history, education (number of completed years of formal education), demographic information, and family history from the informant. Blood pressure, heart rate, respiratory rate, weight, and body temperature were assessed. A standard physical and neurological examination was performed, and extrapyramidal signs were assessed using the modified motor portion of the Unified Parkinson's Disease Rating Scale (Fahn, et al. 1987). The nurse clinician also administered the Geriatric Depression Scale (Hamilton, 1967), the Mild Cognitive Impairment Activities of Daily Living Scale, the Neuropsychiatric Inventory (Galasko, et al., 1997), the Hachinski Ischemic Scale (Hachinski, Iliff, Zilhka, et al., 1975), Physical Activity Scale for the Elderly (Washburn, Smith, Jette, & Janney, 1993), a Leisure Activity assessment (Verghese, et al., 2003), and the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). Apolipoprotein E (apoE) alleles were determined for all participants using restriction enzyme isotyping (Hixson &

Vernier, 1990). A trained psychometrician administered a psychometric battery. Structural MRI was obtained using a Siemens 3.0 Tesla Allegra MRI scanner at the Hoglund Brain Imaging Center located adjacent to the Center on Aging.

The outcome measures included: 1) Physical Activity Scale in the Elderly (PASE) and a modified Community Healthy Activities Model Program for Seniors (CHAMPS): Both questionnaires were used to assess physical activity levels; 2) Physical Performance Test (PPT): This short battery of timed physical tasks was used as a measure of physical function and frailty; 3) Intravenous Glucose Tolerance Test (IVGTT): The primary measures used in analyses were the total area-under-the-curve (AUC) for glucose and insulin which served as the overall indices for glucose and insulin levels. Secondary measures included fasting, 2-hour, and 3-hour post load insulin and glucose levels; 4) Dual energy x-ray absorptiometry (DEXA): this x-ray examination was used to determine fat-free mass, fat mass and percent body fat with participants clothed in a hospital gown; 5) Depressive symptoms: assessed at two year follow up with the Geriatric Depression Scale administered to the study partner; and 6) Two-year interval medical changes: information about medical history and medications were continuously evaluated from the informant during the clinical evaluation. New diagnoses were observed during the two-year follow up period.

The primary results of the Brain Aging Project suggested that early-stage AD is associated with reduced physical performance and habitual levels of physical activity. VO_2^{Max} mean scores were similar between the early AD group (n=31) and the non-demented group (n=31) (19.8 mL/kg/min and 21.2 mL/kg/min, respectively, $p=.26$). There were no group differences in the participant's maximal rating of perceived exertion (PRE), respiratory exchange ratio (RER), and maximal heart rate (MHR) suggesting that individuals with early AD have the

capacity for maximal exercise testing. In addition, there was no direct relationship between cognitive performance measures and cardio-respiratory fitness (Burns, Mayo, Anderson, Smith, & Donnelly, 2008).

The results of the primary study showed that patients with early AD had reduced physical performance and habitual physical activity levels compared to the non-demented group. These findings provided further motivation to investigate the relationship between physical activity levels and physical performance to better understand this phenomenon. Thus we conducted the present study which utilized a retrospective data analysis to investigate any possible association between study variables. The methods of the present study are described as the following:

Research Design

An observational, correlational, longitudinal design was employed to conduct this retrospective study. The research methodology included a secondary data analysis of data collected for the KU Brain Aging Project.

Sample and Setting

One hundred and sixty one participants completed the baseline assessment. Of the 161 participants, 137 completed the follow-up assessment. Among the 137 participants, 25 participants were excluded because of: 1) having an uncertain diagnosis of dementia; 2) having a change in their diagnosis (e.g., non-demented who develop AD); 3) having missing data in the main variables relevant to this study. Among the 25 participants excluded, 7 participants in the non-demented group changed diagnosis (3 participants developed AD and 4 developed uncertain dementia). Participants who maintained the same diagnosis throughout the 2-year follow-up and completed baseline and follow-up assessment were included in the final dataset that was used to conduct the data analysis.

Data from 112 participants were analyzed. The descriptive statistics confirmed the majority of participants were female (57.1%), white (96.4%), non-Hispanic (98.2%), had 16 years of education (25.9%), and were on average 73.8 years old. Forty six participants in the AD group and sixty six participants in the non-demented group completed the baseline and follow-up assessment. Among the AD group, 37 participants had a global CDR score of .5 and the remaining 9 had a score of 1. All the participants in the non-demented group had a score of 0 on the CDR.

Table 1 displays the sample demographic characteristics divided by groups (AD and non-demented). In addition to demographic characteristics, the table also presents both medical and family history for participants in both groups. For example: 36.9% of participants in the AD group were hypertensive compared to 24.2% in the non-demented group, and 47.8% of participants in the AD group had a family history of AD compared to 33.3% in the non-demented group. On-tailed Independent-samples *t*-tests were used to compare groups on demographic characteristics. The results of the *t*-tests showed no significant differences between groups.

Table 1. Characteristics of the sample divided by groups (N = 112).

Variables	Groups		*p* value
	AD (n= 46)	Non-demented (n= 66)	
Age, M (SD)	74.7 (6.9)	73.2 (6.8)	.28
Gender, F (%)			
Male	17 (37.0)	31(47.0)	.29
Female	29 (63.0)	35(53.0)	
Race, F (%)			
White	42 (91.3)	66 (100.0)	
Black or African American	3 (6.5)	-	.08
American Indian or Alaskan	1 (2.2)	-	

Years of Education, M (SD)	15.5 (3.0)	16.5 (2.8)	.07
Body Mass Index, M (SD)	25.5 (4.1)	26.3 (3.9)	.32
Familial History of AD, F (%)	22 (47.8)	22 (33.3)	.10
Smokers, F (%)	1 (2.2)	2 (3.0)	.80
Hypertension, F (%)	17 (36.9)	16 (24.2)	.06
High Cholesterol, F (%) (Cholesterol > 200 mg/dL)	17 (36.4)	17 (25.8)	.77
Diabetes, F (%)	2 (4.3)	-	.16

Note. F = Frequency; M = Mean; SD = Standard Deviation; AD = Alzheimer's disease.

The General Clinical Research Center and the Alzheimer and memory Program in the University of Kansas Medical Center in Kansas City served as the setting for collecting the data.

Research Instruments

In this retrospective study, the main variables were physical activity, cognitive function, and performance of activities of daily living. The instruments used to measure these variables included:

1) The Physical Activity Scale for Elderly (PASE) (Washburn, Smith, Jette, & Janney, 1993).

This scale is composed of 10 questions designed to measure physical activity levels in older adults aged 65 years or older. These questions cover 3 major areas (subscales): 1) personal activities and sports like reading, walking, and jogging; 2) household activities like washing and vacuuming; and 3) work-related activities. Each question contains subordinate questions, for example, questions 1 through 6 contain a multiple choice question followed by an essay part to list all personal activities and sports done during a one-week period. The questions are arranged in each subscale based on the intensity of the activity. The scores on PASE range between 0 and 400. A high score on PASE indicates more practice of physical activity and an active life style.

This instrument was shown to be a valid measure of physical activity in older adults living in the US (Washburn, 1999). It was also tested for validity and reliability on Japanese and Norwegian samples and found to be valid and reliable (Hagiwara, Ito, Sawai, & Kazuma, 2008; Schuit, Schouten, Westerterp, & Saris, 1997). Higher scores on PASE suggest more practice of physical activity and lower scores suggest less activity.

2) The Leisure Activity Assessment (Verghese, et al., 2003).

This instrument is composed of 17 items and 2 major subscales: 1) cognitive activities subscale: items (1-6) represent cognitive activities like reading, writing, and solving crossword puzzles; and 2) physical activities subscale: items (7-17) represent physical activities like playing tennis, swimming, and bicycling. The scale measures the frequency of participation in these activities in a week time ranging from "daily" to "never". The total score of the cognitive activity items (questions 1-6) range from 0 to 42, and the total score of the physical activity items (questions 7-17) range from 0 to 77. A high score on Leisure Activity Assessment indicates more practice and involvement in cognitive and physical leisure activities.

3) Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975).

The MMSE is a brief questionnaire test that is used to screen for cognitive impairment. The scale tests the individual's orientation, calculation, attention, memory, language, and basic motor skills. It is commonly used to screen for dementia, to estimate the severity of cognitive impairment at a given point in time, and to follow the course of cognitive changes in an individual over time. The total score of the MMSE arranges from 0 to 30 points. This instrument is one of the most extensively used and studied clinical assessment Instruments, and was found to be both valid and reliable (Tombaugh, & McIntyre, 1993). A high score on the MMSE denotes better cognitive performance.

<u>4) The Mild Cognitive Impairment-Activities of Daily Living Scale (MCI-ADL) (Galasko et al., 1997).</u>

This instrument was developed in the Alzheimer's Disease Cooperative Study (ADCS) and was used to assess deficits in more complex everyday tasks (Perneczky, et al. 2006). It is composed of 24 questions that assess basic and instrumental activities of daily living in individuals with cognitive impairment. The instrument is divided into two major categories: 1) activities of daily living ADL (questions 1-18), and 2) instrumental activities of daily living IADL (questions 19-24). The overall score on the ADL items varies between 0 (worst performance) and 57 (best performance), and the overall score on the IADL items range from 0 to 16. Higher scores on ADCS-MCI-ADL indicate independence and better performance of ADLs.

In the present study, data collected from study partners in the Brain Aging Project about the participant's physical activity levels (PASE and LAS) and performance of ADLs (MCI-ADL) was used to conduct all data analyses. The cognitive function measure (MMSE) was the only measure that depended solely on the participants' responses and not the study partner. This was applied on both groups in order to obtain from similar sources (study partners). Data collected from participants themselves was not used due to impaired cognitive ability (mainly memory) of participants in the AD group. Impaired memory will negatively affect the accuracy of any self-reported information obtained from individual participants with AD.

Ethical Considerations

The KU Brain Aging Project was approved by the Institutional Review Board (IRB) at the University of Kansas Medical Center. Information about the study was provided to potential participants and families in writing as well as orally. Informed consent was obtained from the

participants or from their primary care givers if the participant was unable to consent

him/herself. Participation in this study was voluntary, and care was taken to protect privacy

information throughout the study. They were informed that the presentation of the results will be

anonymous and information would not be linked to a particular participant.

Data Collection and Management

Data collected through instruments including PASE, LAS, MMSE, and MCI-ADL was

retrospectively analyzed. It was recorded in a separate SPSS file on a computer protected by a

security code, and access to data was limited to authorized personnel. Data were cleaned and

coded before it was analyzed.

Data Analysis

This retrospective study involved a secondary analysis of data collected in the Brain

aging Project. An assistant investigator (Jaber) reviewed these data and performed all necessary

statistical analyses (SPSS, version 17.0). The investigation began with a descriptive analysis of

the main characteristics of the sample and main study variables. The statistical plan also included

both cross-sectional and longitudinal data analyses (Green, & Salkind, 2008).

For question 1, we used parametric tests (*t*-tests) when the assumptions of normality of

distribution and homogeneity of variances are met. We utilized one-tailed paired and

independent-samples *t*-tests to compare group scores on the practice of physical activity,

cognitive performance, and performance of ADLs. Both group scores were compared at baseline

and though follow up. Starting with independent-samples *t*-tests, we compared the mean score of

both groups at baseline and through follow-up separately. We anticipated that the AD group

scores would be less than non-demented group scores in the first hypothesis. For this reason, we

used one-tailed independent-samples *t*-tests by dividing the *p* value obtained from the *t*-tests

results by 2. In addition, we used paired-sample *t*-tests to longitudinally compare the mean score of participants in the same group on the major study variables between baseline and follow-up assessments.

Levene's test of equal variances was significant in some independent-samples *t*-tests conducted on both groups indicating that the variances are unequal, and consequently the group scores variability is different (Portney, L. G. & Watkins, M. P. 2000). To address this problem, we utilized a non-parametric test (Mann-Whitney U) to replace independent-samples *t*-tests for the variables that had a significant Levene's test. In addition, we employed Wilcoxon Signed Rank test (another non-parametric) to replace paired *t*-tests for the same variables that had a significant Levene's test. Using non-parametric tests, we obtained z statistic and used it instead of the t statistics in the *t*-tests' table (table 2).

In question 2, a bivariate correlation analysis assessed the possible association between physical activity (PASE and LAS), cognitive function (MMSE), and performance of ADLs (MCI-ADL) in patients with early stages of AD. In the correlation analysis, we longitudinally assessed the relationship between the major study variables by analyzing the change in scores over the 2-year follow-up period. First, we started by selecting subjects who had high scores (top 50%) on the physical activity measure PASE at baseline in each group separately. Because we ranked the PASE scores smallest to largest and used data from participants who scored among the top 50%, 23 participants in the AD group and 33 in the non-demented group entered the correlation analysis. Second, we calculated the change in scores for all major study variables by subtracting the baseline (T1) score from the follow-up (T2) score ($\Delta T = T2 - T1$). Third, we entered the new variables which contain the score change into the correlation analysis to obtain the Pearson correlation coefficients that express the strength and direction of relationship

between the variables. Fourth, we conducted a partial correlation analysis to control for demographic characteristics that may act as confounders (age, gender, and education). For example: age was controlled for because AD is an age-dependant disease (Sevush, Leve, & Brickman, 1993). Both age and gender were significantly associated with cognitive decline in this study ($p < .05$) and through literature (Buckwalter, et al., 1996; Celsis, et al., 1997; Li, et al., 2009). Educational level might serve as a confounder (Bennett, et al., 2003; Roe, Xiong, Miller, & Morris, 2007; Scarmeas, Albert, Manly, & Stern, 2006), and were controlled for as well. We reported the partial correlation coefficients after controlling for age, gender, and educational level.

For question 3, we utilized a multiple regression analysis to assess the predictive relationship of cognitive function (MMSE) to performance of ADLs (MCI-ADL) in the AD group. We used the AD's group baseline scores on the MMSE with change in MCI-ADL score of the MCI-ADL over the 2-yaer follow-up period. If cognitive function predicts performance of ADLs, then we expect to find a negative correlation between the MMSE baseline scores and change in total scores of MCI-ADLs. This means that the higher cognitive function is associated with less change in the performance of ADLs (less functional decline). In the regression analysis, the effect of age, gender, and educational level was controlled for by placing these variables in the first model of the multiple regression. In the second model, baseline MMSE score was added to the age, gender, and educational level. By doing this, effects of the demographic characteristics that may influence the predictive relationship of cognitive function were isolated. Before running the regression analysis, variables were tested for normality, independence, co-linearity, and variance equality in order not to violate any of the assumptions of the regression analysis.

Results

Characteristics (mean and standard deviation) of the main variables (MMSE, MCI-ADL, PASE, and LAS) for both groups are displayed in table 2. The table also displays the subscales of PASE (personal activities subscale, household activities subscale, and work-related activities subscale) and LAS (cognitive activities subscale and physical activities subscale) in addition to the total scores of both scales. The table also contains group comparisons at baseline and follow up assessments.

Table 2. Group comparisons (between and within groups) at baseline and follow-up (N = 112)

Variables	Groups					
	AD (n= 46)			Non-demented (n= 66)		
	M	SD	*p* value	M	SD	*p* value
MMSE Baseline*	25.61	3.22		29.43	.78	.000
MMSE Follow-up*	21.18	7.59		29.18	1.31	.000
Δ MMSE*	- 4.42	5.96	.000	- .27	1.09	.032
ADCS– MCI–ADL Baseline*	40.37	7.26		49.10	2.53	.000
ADCS– MCI–ADL Follow-up*	32.78	12.50		49.66	2.24	.000
Δ ADCS– MCI–ADL*	- 7.58	9.84	.000	.56	2.68	.048
PASE Total Score Baseline	82.49	54.04		125.23	63.19	.000
PASE Total Score Follow-up	59.95	43.89		117.19	55.57	.000
Δ PASE Total Score	- 22.53	55.63	.005	- 8.03	54.13	.205
a- Personal Activities Subscale Baseline*	14.27	18.5		22.88	25.52	.027
Personal Activities Subscale Follow-up*	6.46	9.29		15.53	26.82	.015
Δ Personal Activities Subscale*	- 7.81	16.60	.001	- 7.35	35.83	.001
b- Household Activities Subscale Baseline	57.47	35.81		78.62	38.76	.002
Household Activities Subscale Follow-up	47.73	37.42		81.00	42.78	.000
Δ Household Activities Subscale	- 9.73	41.07	.058	2.37	33.92	.286
c- Work-related Activities Subscale Baseline*	10.73	30.74		23.72	41.63	.001
Work-related Activities Subscale Follow-up*	5.73	15.68		23.54	40.73	.001

	M	SD	p	M	SD	p
Δ Work-related Activities Subscale*	- 5.00	29.36	.174	- .18	31.75	.383
LAS Total Score Baseline	19.41	7.66		24.12	8.91	.002
LAS Total Score Follow-up	13.97	7.98		21.93	7.74	.000
Δ LAS Total Score	- 5.43	8.79	.000	- 2.18	8.05	.016
a. Cognitive Activities Subscale Baseline	10.19	6.07		12.31	4. 85	.022
Cognitive Activities Subscale Follow-up	7.95	5.13		13.22	5.04	.000
Δ Cognitive Activities Subscale	- 2.23	5.19	.003	.90	4.69	.061
b. Physical Activities Subscale Baseline*	9.21	4.69		11.80	6.65	.017
Physical Activities Subscale Follow-up*	6.02	4.85		8.71	5.57	.005
Δ Physical Activities Subscale*	- 3.19	6.23	.001	- 3.09	6.42	.001

Note. M = Mean; SD = Standard Deviation; MMSE = Mini Mental State Examination; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living; PASE = Physical activity Scale for Elderly; LAS = Leisure activities Scale; Δ Score = Follow-up score – Baseline score; AD = Alzheimer's disease; * = *t*-test replaced with a non-parametric test (Man-Whitney U and Wilcoxon Signed Rank test).

Decline in Cognition, Function, and Practice of Physical Activity

Group scores were compared using one-tailed independent and paired *t*-tests to evaluate the first hypothesis that the groups' scores were not equal on the main study variables (MMSE, MCI-ADL, PASE, and LAS). Table 2 displays the baseline and follow-up comparisons of group scores obtained through independent *t*-tests. The AD group had significantly lower scores than the non-demented group at baseline and follow-up assessments ($p < .027$). For example, participants with AD scored lower than non-demented participants on the MMSE at baseline ($z = -7.40$, $p < .001$) and through follow-up ($z = -8.18$, $p < .001$). Similar to MMSE, the AD group also scored lower on the ADLs measure MCI-ADL ($z = -7.44$, $p < .001$) and physical activity measures PASE ($t = 3.37$, $p < .001$) and LAS ($t = 2.90$, $p = .004$) than the non-demented group at baseline. The follow-up comparison of group scores showed consistent results with baseline comparison on MCI-ADL ($z = -8.37$, $p < .001$), PASE ($t = 5.83$, $p < .001$), and LAS ($t = 5.28$, $p < .001$).

Paired *t*-tests longitudinally compared the mean score of participants in the same group on the major study variables between baseline and follow-up assessments. The results indicate participants in the AD group scored significantly lower at the follow-up assessment compared to the baseline assessment ($p < .005$). However, the non-demented group scored significantly lower only on the LAS total score, physical activities component of LAS, and personal activities component of PASE ($t = 2.19, p = .016; z = -3.45, p = .001; z = -3.09, p = .001$, respectively). While the AD group participants showed significant decline in their ability to perform ADLs ($z = -4.59, p < .001$), the non-demented group maintained the same level of functional performance of ADLs with a slight, significant increase in the mean difference between baseline and follow-up on the MCI-ADL at follow-up ($z = -1.66, p = .048$). Figure 1 presents a comprehensive comparison of mean scores between and within groups at baseline and through follow-up.
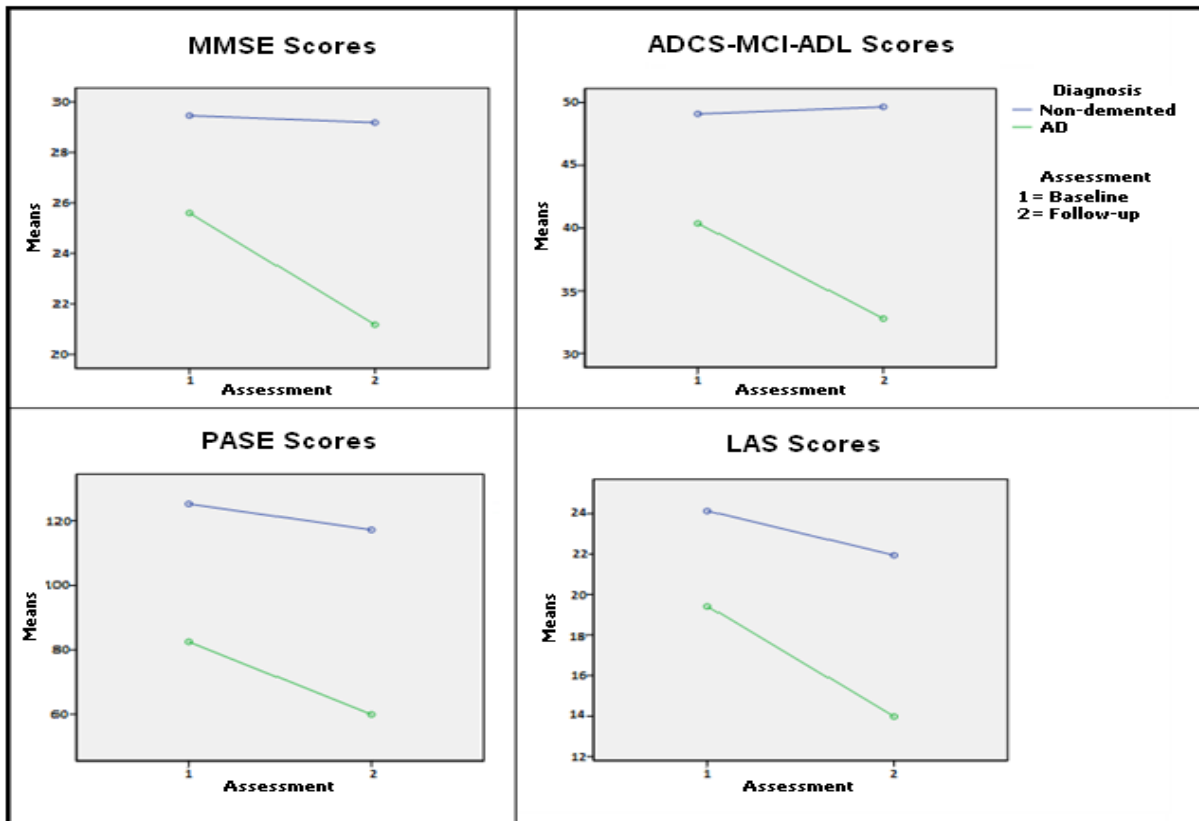

Figure 1. Comparison of mean group scores on major study variables between the AD and non-demented groups. Baseline and follow-up assessments are separated by a 2-year gap (N = 112).

It should also be noted that the AD group lost on average 4.42 points on the MMSE compared to .27 points in the control group during 2 years. Based on the t-tests' results, we reject the null hypothesis that the group scores are equal as we have seen a clear and significant drop in the participants scores over the course of 2 years.

Association between Physical Activity, Cognitive Function, and Performance of ADLs

A correlation analysis tested the second hypothesis about the relationship between physical activity, cognitive function, and performance of ADLs. The results showed a significant positive association between change in leisure activities and change in the performance of ADLs in the AD group. For instance, the partial correlation coefficient (r) between change in the LAS total score and the MCI-ADL total score was .43 ($p < .01$). The physical activities component of LAS was significantly and positively correlated with change in the MCI-ADL total scores ($r = .40, p < .01$), but not the cognitive activities component ($r = .23, p = .13$). Change in PASE subscales and total score had a weak positive correlation that did not achieve significance with change in MCI-ADL scores except for the household activities component of PASE ($r = .30, p = .05$). Change in cognitive function represented by MMSE scores was correlated positively and significantly with change in performance of ADLs ($r = 71, p < .01$).

Tables 3 and 4 display the partial correlation coefficients of the major study variables' score change after controlling for age, gender, and educational level for both AD and non-demented groups.

Table 3. Correlation Matrix of the Partial Correlation between change in scores of the major study variables after controlling for age, gender and educational level for the AD group (n = 23).

Variable	1	2	3	4	5	6	7	8	9
1. Δ MMSE	1.00								
2. Δ PASE-Personal sub.	.01	1.00							
3. Δ PASE-Household sub.	.28	-.15	1.00						
4. Δ PASE-Work sub.	-.06	.11	.13	1.00					
5. Δ PASE Total Score	.17	.25	.75**	.67**	1.00				
6. Δ LAS-Cognitive sub.	.30*	-.06	.22	-.14	.07	1.00			
7. Δ LAS-Physical sub.	.22	.34*	.19	.39*	.46**	.12	1.00		
8. Δ LAS Total Score	.34*	.20	.28	.19	.37*	.70**	.79**	1.00	
9. Δ ADCS-MCI-ADL	.71**	.08	.30*	-.08	.20	.23	.40**	.43**	1.00

Note. * *p* < .05; ** *p* < .01; Δ = Change in scores over the 2-year follow-up period; Sub = Subscale; MMSE = Mini-Mental State Examination; PASE = Physical Activity Scale for Elderly; LAS = Leisure Activities Scale; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living.

Table 4. Correlation Matrix of the Partial Correlation between change in scores of the major study variables after controlling for age, gender and educational level for the non-demented group (n = 33).

Variable	1	2	3	4	5	6	7	8	9
1. Δ MMSE	1.00								
2. Δ PASE-Personal sub.	-.05	1.00							
3. Δ PASE-Household sub.	-.09	-.09	1.00						
4. Δ PASE-Work sub.	-.02	.06	-.00	1.00					
5. Δ PASE Total Score	-.12	.32*	.62**	.61**	1.00				
6. Δ LAS-Cognitive sub.	.01	-.12	-.03	.21	.03	1.00			
7. Δ LAS-Physical sub.	.07	.02	-.18	.02	-.06	-.01	1.00		
8. Δ LAS Total Score	.07	-.05	-.16	.14	-.02	.57**	.81**	1.00	
9. Δ ADCS-MCI-ADL	-.08	.10	-.01	.11	.10	.09	.16	.18	1.00

Note. * *p* < .05; ** *p* < .01; Δ = Change in scores over the 2-year follow-up period; Sub = Subscale; MMSE = Mini-Mental State Examination; PASE = Physical Activity Scale for Elderly; LAS = Leisure Activities Scale; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study-Mild Cognitive Impairment-Activities of Daily Living.

As shown in table 4, the non-demented group did not show any significant correlation between physical activity and ADLs. Change in the total score of the physical activity measures (PASE and LAS total scores) were not correlated significantly with change in the MCI-ADL total score ($r = .10$, $p = .41$; $r = .18$, $p = .14$, respectively). Additionally, the partial correlation coefficient between the total score of the MCI-ADL scale and the MMSE showed a negative trend that did not attain significance ($r = - .08$, $p = .50$).

Cognitive Function as a Predictor of Change in the Performance of ADLs

A multiple regression analysis was conducted to test third hypotheses that cognitive function may predict better performance of ADLs in individuals with early stages of AD. The first model included three demographic characteristics (age, gender, and education), and the regression analysis showed that these demographic characteristics did not predict change in the performance of ADLs ($R2 = .04$, adjusted $R2 = -.02$, $F (3, 42) = .687$, $p = .54$). The second model included the baseline MMSE scores, and regression analysis revealed that baseline cognitive function predicted change in performance of ADLs over 2 years ($R2$ Change $= .21$, adjusted $R2 = .18$, $F (1, 41) = 3.60$, $p =.001$) after controlling for the effect of the demographic characteristics. Table 5 displays the results of the multiple regression analysis.

Table 5. Predictive relationship of cognitive function and change in performance of ADLs after controlling for age, gender, and education in the AD group ($N = 46$).

Variable	Model One β	Model Two B
MMSE baseline score	-	-.47**
R	.22	.51
R^2	.05	.26
Adjusted R^2	-.01	.19
R^2 Change	.21	-

Variable	Model One β	Model Two B
F Change	.73	11.97

Note: ** = *p* < .01; MMSE = Mini Mental State Examination.

Discussion

The findings of this study suggest that individuals in the early stages of AD demonstrate significant declines in cognitive function and functional performance of ADLs over 2 years. Individuals with AD also showed less engagement in physical activity and leisure activities. By contrast, older adults in the control group showed significant decline in cognition but not in function. Although both groups exhibited reduced performance, the rate of decline was faster in individuals with AD. Given that cognitive decline and functional decline are age-related processes, the AD group had the added disadvantage of the disease presence which may have increased the rate of decline in both cognition and function among people with early-stage AD. These findings supported the hypothesis that individuals with AD would exhibit more decline in cognitive function, performance of ADLs, and practice of physical activity. These findings are also consistent with the findings of other studies in the literature.

In addition, leisure activities were significantly associated with cognitive function and performance of ADLs only in individuals with AD not older adults. Change in the practice of leisure activities was positively associated with cognitive decline and functional decline. More specifically, the physical activities component of the leisure activities was significantly associated with cognitive and functional decline. In other words, people who demonstrated less practice of leisure activities also showed a reduced cognitive ability and less capability to perform ADLs over the period of 2 years. One interpretation of this phenomenon is that leisure activities may have some beneficial influence on cognition, and this may attenuate the decline in

function. Another interpretation is that cognitive decline might have been the main trigger that caused decline in functional performance of ADLs and less practice of leisure and physical activities at the same time.

Physical activity represented by PASE total scores was not significantly associated with cognitive function and performance of ADLs in both groups. The results showed that reduction in physical activity was not associated with cognitive and functional declines. Only the household activities component of PASE have shown to be significantly associated with decline in cognitive performance and performance of ADLs in individuals with AD. This association might be explained by the fact that both scales assess relatively similar activities. For example, the household activities component of PASE includes light and heavy housework, home repairs, lawn work, outdoor gardening, and caring for others (Washburn, Smith, Jette, & Janney, 1993). Similarly, the MCI-ADL includes activities like cleaning a room, doing laundry, and using household appliances (Galasko et al., 1997). These similarities may have led to a stronger association compared to other subscales of PASE.

Cognitive function significantly predicted change in the performance of ADLs in individuals with early AD. Individuals with AD who had better cognitive capability at baseline demonstrated less functional decline in the performance of ADLs over the 2-year follow-up period. Supporting this conclusion is the strength of bivariate correlation coefficient (r) between the baseline cognitive function and change in ADL performance, which was -.46, $p = .001$, as well as the comparable partial correlation coefficient that isolated the effect of age, gender, and education, which was -.47, $p = .001$. This finding supports the hypothesis that cognitive function predicts performance of ADLS in AD, and supports the findings of another study that addressed this relationship in the literature (Arcoverde, et al., 2008). Cognitive function predicted onset of

limitations in ADLs in a group of community dwelling older adults (Dodge, et al., 2004; Moritz, Kasl, & Berkman, 1995). Mariani et al 2008 conducted a study on individuals with mild cognitive impairment (MCI) and concluded that a mild degree of cognitive deterioration has a stronger impact on IADL.

The findings of the present study were consistent the findings of another study. Arcoverde et al (2008) conducted a cress-sectional study to evaluate the relation between the practice of physical activity, cognition, and activities of daily living (ADL) in patients with AD. The results showed that the active AD group presented with the same degree of dependence as found in sedentary AD patients given the fact that participants in the sedentary AD group were on average 10 years younger than participants in the active AD group. Both studies support the notion that physical may be beneficial for individuals with AD as it may contribute to decreased cognitive or functional decline.

In summary, individuals in the early stages of AD exhibit faster rates of cognitive and functional decline than older adults without AD. This is due to the changes associated with the progress of AD in addition to the commonly well-known age-related changes. Household activities and physical leisure activities are associated with cognitive function and performance of ADLs. More engagement in these activities may attenuate or influence the rate of cognitive and functional decline in individuals with AD. Finally, more research should be done involving more rigorous designs like randomized controlled trials to investigate the relationship between physical activity and performance of ADLs in AD. Also, this relationship should be investigated in different stages of AD to determine any possible influence of physical activity on functional performance and independence at different stage of the disease.

Study Limitations

A few limitations of the present study should be noted. One limitation is the relatively small sample size may have affected the results of this study. A power analysis indicated that we needed 64 participants in each group to perform group comparisons. The number of participants in the AD group (n = 46) did reach that goal. This occurred due to the dropouts (24 participants) and the exclusion of another 25 participants who were not eligible to be entered to the data analysis. Another limitation is presence of some possible confounders (e.g. hypertension, diabetes) that may have affected our results. Evidence from literature shows that co-morbidities like hypertension (Bellew, et al., 2004), diabetes (Ravona-Springer, et al., 2010), and depression (Fitz & Teri, 1994; Geerlings, et al., 2000) affect the rate of cognitive decline in AD. A third limitation is the recall bias that is normally associated with the use of self-reported instruments. For example, in PASE, subjects and study partners were asked to report the frequency of physical activity done in the past 7 days. This may vary depending on many factors like the individual's cognitive ability and various environmental factors.

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Appendix A

The Association between Physical Activity, Cognitive Function, and Performance of Activities

of Daily Living in Patients with Early Alzheimer's Disease

Comprehensive Literature Review

BY

Ala'a F. Jaber, OT

Alzheimer's disease

AD is the sixth major cause of death in the United States and the most common cause of dementia, accounting for 50-70% of the cases. About 5.3 million people aged 65 years and older in the United States are living with AD, and by 2050 this number could increase up to 16 million (Alzheimer's Association [AA], 2009; American Health Assistance Foundation [AHAF], 2009). AD is also a common disease worldwide with an estimated 18 million people affected, and by 2050, this figure is projected to grow to nearly 34 million (World Health Organization [WHO], 2006). In the state of Kansas, rates of Alzheimer's hospitalization for elderly aged 65 years and older were approximately 137 people per 100,000 in 2003, and the age-adjusted mortality rates due to AD were about 20 deaths per 100,000 in 2007 (Kansas Department of Health and Environment [KDHE], 2005; KDHE, 2009). Patients with AD live approximately 10 years after an established diagnosis of the disease. The actual cause of death in AD patients is not the disease itself but rather other complications such as pneumonia, heart attacks, complications from a fall, or urinary tract infections.

Costs for care for patients with AD and other forms of dementia are significant for families and health care agencies in general (Graff, et al., 2006). The total annual AD burden in the United States is estimated to be $164 billion including costs of care and lost wages (AA, 2009). These costs are typically divided into formal and informal costs. Formal costs are the dollars spent on services provided in a formal health facility including physician visits, emergency room visits, acute hospitalization, and long-term care (Max, 1993). Informal costs are the value of unpaid care provided to the patient like care provided by caregivers. The annual costs for formal care average $27,672 per patient, and the annual informal care costs are approximately $22,458 per patient (Rice, et al., 2001).

The causes of AD are still not clear, and there are 3 major hypotheses that explain the causes of the disease: the amyloid hypothesis, the tau hypothesis, and the cholinergic hypothesis. The amyloid hypothesis is the predominant model that explains the molecular pathogenesis in AD (Mudher & Lovestone, 2002). According to this hypothesis, the neural degeneration in AD is caused by deposition and accumulation of Amyloid β-peptide (Aβ) in plaques in the brain tissue (Hardy & Selkoe, 2002). Aβ peptide is derived from the amyloid precursor protein (APP). Two enzymes called β-amyloid cleaving enzyme (BACE) and γ-secretase cleave the APP to produce the Aβ peptide which is later released to accumulate in plaques in the brain tissue leading to the degeneration and death of neurons. The Aβ peptide induces the subsequent pathology that includes protein tau aggregation, phosphorelation, and clinical dementia (Mudher & Lovestone, 2002). The formation of neurofibrillary tangles that contains tau protein is proposed to result from an imbalance between Aβ peptide production and clearance from the brain tissue.

The second hypothesis is the tau hypothesis. The major assumption of tau hypothesis of AD neurodegeneration is that by converting normal tau protein into a functionally-impaired paired helical filament (PHF) tau, microtubules found in the nerve axons would become unstable, thus disrupting the microtubule-based axonal transport. Consequently, the affected neurons fails to export proteins from the cell body to distal processes and to retrieve substances internalized at axon terminals and this would compromise the function and viability of these neurons. These events end by neuronal dysfunction and degeneration, leading to the onset or progression of AD (Trojanowski, & Lee, 2006). The function of the normal tau is to connect and stabilize the microtubules found in the nerve cells' axons, and thereby maintaining the network of microtubules that are essential for axonal transport in neurons (Forman, Trojanowski, & Lee, 2004). However, the phosphorelation of tau negatively affects the tau's ability to bind to

microtubules, and in the affected neurons, microtubules will be gradually replaced by neurofibrillary tangles (Gray, Paula-Barbosa, & Roher, 1987). Thus, abnormally phosphorylated tau, known as the paired helical filaments (PHFs) at the amino acid level, was identified as the building blocks that form AD's neurofibrillary tangles (Lee, Balin, Otvos, & Trojanowski, 1991). The tau hypothesis also argues that the neurfibrillary tangles are central to AD. This was supported by the fact that tangles arise in the neuron then accumulate to occupy much of the neuron leading to neuronal death. Neurofibrillary tangles also are found abundantly in the brain of patients with AD in late stages of the disease (Mudher & Lovestone, 2002).

The cholinergic hypothesis was first introduced in 1982 (Bartus, Dean, Beer, & Lippa, 1982), and was based on the assumption that some AD symptoms are due to a deficiency of the neurotransmitter acetylcholine (ACh) in the brain (Bowen, Smith, White, & Davison, 1976; Davies, & Maloney, 1976). This hypothesis states that a malfunction of the cholinergic system in the brain contributes significantly to the cognitive decline and behavioral changes observed in patients with AD (Dringenberg, 2000; Terry, & Buccafusco, 2003). This hypothesis has served as the basis for most treatment strategies and drug development approaches for AD to date. The neuropsychiatric symptoms of AD have been linked to cholinergic deficiency, and the use of cholinergic drugs alleviated behavioral disturbances observed in patients with AD. This provides the basis for the cholinergic hypothesis of the neuropsychiatric symptoms of AD (Cummings, & Back, 1998). The validity of this hypothesis has been challenged by the results of a study of early AD (Davis et al., 1999) that reported a preserved activity of cholineacetyltransferase (ChAT) or acetylcholinesterase (AChE), and no evidence of deficiency of ChAT or AChE was found (Terry, & Buccafusco, 2003).

Neuritic plaques, neurofibrillary tangles, and loss of connections between neurons responsible for memory and learning are the three major hallmarks found in the brain of AD patients (National institute of neurological disorders and stroke [NINDS], 2009). Plaques are commonly found in the brains of the elderly but they appear in excessive numbers in the brains of AD patients. Tangles are abnormal filaments comprised of the hyperphosphorelated and aggregated form of the microtubules associated with protein tau. Plaques and tangles are found in areas of the brain such as the hippocampus, basal forebrain, the amygdale, and entorhinal cortex of AD patients.

The consequences of AD are devastating. The plaque and tangle accumulation in the brain tissue causes nerve-cell damage and death. Nerve damage begins by effecting areas of memory and learning in the brain. This damage gradually expands to areas of thinking, judgment, and behavior causing a steady and gradual cognitive decline. This decline starts by memory lapses, forgetting names or the location of keys, eyeglasses, or other everyday objects. Memory problems develop and friends, family, or co-workers begin to notice it. In early to moderate stages of AD, major gaps in memory and deficits in cognitive function emerge leaving the patient in need for some assistance in daily activities. For example, patients become unable to remember their home address or telephone number, and may require help to choose proper clothes for a season or occasion. In severe stages of AD, patients suffer from significant personality changes and need extensive help with daily activities. Eventually, patients become completely dependent as they lose their ability to respond to the environment, to speak, and to control movement (AA, 2007). Although AD is an incurable disease, early diagnosis and initiation of treatment are considered key elements for delaying the progression of the disease and thus early loss of independence (Fuchsberger, Padberg, Faltraco, Moller, & Hampel, 2002).

AD's defining features include progressive cognitive impairment and non-cognitive behavioral abnormalities like depressed mood, agitation, and hostility (Folstein, et al., 1999; Zubenko, et al., 2003). Cognitive impairment often is the most evident consequence of AD, and therefore has been the major concern of treatment and rehabilitation. The healthy brain tissue degenerates causing a steady decline in memory and mental abilities. Eventually, this decline affects the patient's ability to perform daily activities leading to dependence in severe stages of the disease. Furthermore, patients who suffer from dementia have significant problems in remembering recent events. They can also have decreased problem solving abilities, impaired judgment, poor insight, difficulties with abstract thinking and processing information, and poor safety awareness. Consequently, they may become less independent in a wide range of occupations, including activities of daily living, work, leisure, and social participation (Levitt, 2007). Increased dependence in the activities of daily living is the most common problem that develops as the symptoms of AD progress because increased dependence severely limits the quality of life of persons with AD and often the caregivers (Rive et al., 2005). As a result, there is a need for supportive strategies to assist in maintaining the person's independence and safety for as long as possible (American Occupational Therapy Association [AOTA], 2008).

AD is a progressive and terminal disease. The average life expectancy for a person with Alzheimer's is 7 to 10 years after the onset of symptoms at the age of 60 to 70 years (Zanetti, Solerte, & Cantoni, 2009). Also, it may be as low as 3 years for individuals diagnosed in the ninth decade of their life. However, the course of the disease varies from person to person and individuals with AD may live up to 20 years. AD is not the direct cause of death but rather other complications such as pneumonia, heart attacks, complications from a fall, or urinary tract infections. While AD may not be the direct cause of death, poor health and sedentary lifestyle of

a person with AD may increase the risk of serious infections like pneumonia. Other diseases associated with old age (heart disease and cancer for example) may lead to more severe consequences in persons with AD.

<center>Activities of Daily Living</center>

Activities of daily living (ADLs) are the activities we perform in our daily routines. These activities are oriented toward self care and are considered fundamental to living in a social world (Christiansen, & Hammeker, 2001; Rogers, & Holm, 1994). According to the occupational therapy frame of reference (Roley, et al., 2008), ADLs include dressing, eating, feeding, bathing and showering, bowel and bladder management, functional mobility, personal device care, sexual activity, personal hygiene and grooming, and toilet hygiene.

Instrumental activities of daily living (IADLs) are the activities that individuals perform to support daily life within the home and community (Roley, et al., 2008). IADLs include care of others, care of pets, child rearing, communication management, community mobility, financial management, health management and maintenance, home establishment and management, meal preparation and cleanup, religious observance, safety and emergency maintenance, and shopping. These activities often require more complex interactions than self-care used in ADL.

ADLs and IADLs require many skills and abilities. For example, a person may require a variety of physical abilities (such as adequate strength, endurance, and range of motion (ROM)) to accomplish a certain task. In addition to physical abilities, ADLs require appropriate cognitive abilities like memory, problem solving, abstract thinking, and decision-making skills. Also, ADLs require adequate sensory-perceptual abilities to function and interact with the environment like vision, touch, and hearing. All of these abilities can be affected by normal aging as well as different diseases and disorders.

When working with people who have disability, occupational therapists are concerned with the client's independence in the activities daily of living. Occupational therapy treatment goals for people with AD include maintaining the individual's functional performance, promoting participation in activities that enhance physical and mental well being, and facilitating caregivers' participation in providing care (Crepeau, Cohn, & Boyt Schell, 2008). It therefore is important to conduct research studies to better understand mechanisms governing how the disease progresses as well as to improve the efficacy of intervention plans.

Occupational therapists are also considered with the health and well-being of caregivers of patients with AD. Family members and friends who later become caregivers are also affected by the disease. AD has an impact upon the lives of caregivers who carry new responsibilities as patients progress toward dependence. Caring for a patient with AD may cause emotional, psychological, and physical problems. In fact, 24% of caregivers of Alzheimer's patients go to the emergency room or are hospitalized because they had depressive symptoms due to providing care for AD patients who suffer from behavioral and psychological symptoms (BPSD) (Schubert, et al., 2008). Care-giving for patients with dementia has been associated with increased levels of depressive symptoms and a higher prevalence of clinical depression and anxiety (Connell, Janevic, & Gallant, 2001). Psychotropic drug-use was also higher among caregivers than non-caregivers (Schulz, O'Brien, Bookwala, & Fleissner, 1995). Caregivers often find themselves isolated from friends and regular social activities. Furthermore, they struggle with guilt over feelings of resentment or frustration that arise as they cope with a loved one who develops difficult abnormal behaviors.

Health care professional must also consider the burden that falls on caregivers. A variety of researchers have conducted qualitative and quantitative studies to describe and measure

caregiver's burden (Bell, Araki, & Neumann, 2001; Bullock, 2004; Croog, Burleson, Sudilovsky, & Baume, 2006; Farcnik & Persyko, 2002; Rymer, et al., 2002; Spadin, 2008; Teri, 1997). As AD patients become less independent, there is increased responsibility for caregivers to provide support and help in performing activities of daily living. Assuming these responsibilities increases stress for caregivers, as they try to cope with difficulties associated with caring for people with AD in addition to other stress-inducing factors like income reduction and emotional issues (Dooley & Hinojosa, 2004; Graff, et al., 2006). Caregivers who express greater emotional stress and feelings of being "stuck" with care responsibilities were more likely to admit persons with dementia to nursing homes (Gaugler, Yu, Krichbaum, & Wyman, 2009). Moreover, patients' quality of life worsens as they become more dependent on caregivers, and maintaining independence for as long as possible improves the quality of life of patients with AD (AOTA, 2008).

AD poses financial problems for caregivers as well. Studies on the financial impact of the disease have found that the average caregiver with a full-time job will miss more than 3 weeks of work per year. Moreover, about 9.9 million caregivers –children, other family members, friends, and neighbors- provided 8.5 billion hours of unpaid care in 2008, which amounts to approximately $94 billion in value (AA, 2009). These costs increase the burden on caregivers of AD patients and may lead to stress or other undesired outcomes.

More than 90% of AD patients live at home either alone, with their families, or with caregivers (Dooley & Hinojosa, 2004; Nygard & Stakhammer, 2003). They may also be admitted to assisted living facilities or nursing homes, including dementia care units. In 2004, the number of AD patients admitted to nursing homes was 126,600 with an average length of stay of 944 days (Center for Disease Control and Prevention [CDC], 2008). In an attempt to study this

phenomenon, Gaugler et al (2009) explored the predictors of nursing home admission for persons with dementia. The results showed that reduced independence in basic activities of daily living, severity of cognitive impairment, and a diagnosis of AD were the major predictors for admission to care facilities. Understanding factors that contribute to the severity of AD helps health professional take necessary precautions to delay progression of the disease, and the potential admission to a nursing home or another care facility.

Alzheimer's patients are particularly vulnerable to neglect and abuse by caregivers or at nursing homes. The results of a recent literature review confirmed that frail adults over 75 years of age who have a diagnosis of dementia are at heightened risk of mistreatment (Fulmer, 2008). Patients with AD lose their ability to remember, to follow instructions, and to control their own behaviors as the disease progress, and consequently they are more susceptible to neglect and abuse. Neglect and abuse of Alzheimer's patients can take many forms. For example: Patients with AD may wander away from their ward or off the nursing home campus entirely placing them at risk of injury from traffic, falls, and exposure to the elements. Another form of abuse is the physical abuse and neglect. Some staff members in the nursing home may lose their tempers and verbally or physically abuse an Alzheimer patient. Others may neglect the needs of people with Alzheimer's rather than engage with a difficult patient. Patients with AD residing in a nursing home are also at risk of abuse from other residents because the AD patients may have unknowingly encouraged attacks by walking into someone's bedroom invading other resident's personal space, or eating from another resident's plate. Further, caregiver's abuse has been reported, it took the form screaming or yelling at a patient with AD, insults or swearing, and threats of sending the person to a nursing home. Delaying the onset of AD symptoms will delay

patient's institutionalization or admission to nursing homes, and eventually may reduce the incidence of neglect or abuse.

<div align="center">Physical Activity</div>

Physical activity can be defined as any movement that requires energy expenditure and is produced by the body's skeletal muscles (WHO, 2009b). Metabolic Equivalents (METs) are commonly used to express the intensity of physical activity. A MET is defined as the ratio comparing an individual's metabolic rate while sitting quietly to his metabolic rate while performing a certain task (American Heart Association [AHA], 2009). Another definition of the MET is the energy spent during resting or sitting quietly, and is equal to a caloric consumption of 1 kcal/kg/hour.

Physical activity has been documented to play an important role in a healthy lifestyle (Stewart 2005). In this essence, researchers studied the effect of physical activity on older adults, and many studies supported the argument that physical activity is beneficial for the health of the elderly (Stewart, 2005; Vogel, et al., 2009; Warburton, Nicol, & Bredin, 2006). These benefits include reducing mortality due to cardiovascular problems or stroke (Bijnen, et al., 1998; Fried, et al., 1998), optimizing blood pressure (Whelton, Chin Xin, & He, 2002), reducing the incidence of type 2 diabetes and lowering prevalence of glucose intolerance (Laaksonen, et al., 2005; Ryan, 2000; Van Dam, Schuit, Feskens, Seidell, & Kromhout, 2002), and helping to prevent breast cancer (Friedenreich, 2001), hypertension (Kokkinos, Narayan, & Papademetriou, 2001), stroke (Hu, et al., 2000) and hip fractures (Cavill, Kahlmeier, & Racioppi 2006).

Other studies have shown that physical activity may be an important part of maintaining independence in older adults. Brach et al. (2003) studied the association between physical activity and function in a sample of two hundred twenty-nine older women (mean age of 74.2

years) and concluded that physical activity plays a role in maintaining functional ability later in life. Additionally, a program of physical activity in the elderly enhances muscle strength, and therefore limits the incidence of disability and maintains independence in daily living (Vogel, et al., 2009). Physical activity reduces the rate of motor performance decline associated with normal aging (Visser, Pluijm, Stel, Bosscher, & Deeg, 2002).

Studies of physical activity and aging utilized different types of activities and exercises with different intensities. For example: aerobic or endurance exercises, balance training, flexibility exercises, and progressive resistance training (Binder, et al., 2005; Vogel, et al., 2009). One study examined the effect of endurance programs/aerobic exercises that targets cardio-respiratory fitness on older adults (Malbut, Dinan, & Young, 2002). Fitness was measured via maximal oxygen consumption (VO_2^{Max}) which is defined as the maximum capacity of an individual to utilize oxygen during incremental exercise, and is measured in "mL/kg/min" which stands for milliliters of oxygen used in one minute per kilogram of body weight. Aerobic exercises include swimming, walking, jogging, and gardening. The benefits of aerobic or endurance training include maintaining and improving cardiovascular functions, whereas strength training helped counterbalance the loss in muscle mass and strength associated with aging. In addition, regular exercise resulted in higher bone density and reduced risk of osteoporosis, enhanced postural stability, and increased flexibility (Stewart, 2005).

Some of these studies have examined the association of physical activity with the risk of AD and related dementias in older adults. Higher levels of physical activity (exercising 3 or more times per week at intensities greater than walking) were associated with a reduced incidence of AD by 50% among a group of dementia-free people (Laurin, Verreault, Lindsay, Macpherson, & Rockwood, 2001). Abbott et al (2004) study results confirmed the findings of Lauren et al

(2001). The investigators examined the association between walking and the risk of developing

dementia in a group of older adult (Age≥70 years). The results suggest that those who walk less

than 0.25 miles per day have more than double the odds of developing dementia compared to

those who walk 2 miles per day. These findings underpin the benefits of physical activity on

reducing the risk of developing dementia among older adults (Abbott, et al., 2004). In a third

study, Yoshitake et al (1995) reported that physically active subjects are 4 times less likely to

develop AD than non-physically active subjects (RR = .20), and concluded that physical

activity, such as regular exercise and moderate or intense physical work, may be useful for the

prevention of AD. Moreover, in a longitudinal study, a cohort of individuals aged 65 years or

older persons reported the frequency and type of leisure activities. The results showed that

engaging in stimulating activities (e.g., playing cards, practicing art, and going to movie theaters)

at least twice a week reduced the risk of developing dementia by 50% over the 4-year follow-up

period compared to individuals who engaged similar activities less than once a week (Akbaraly,

et al., 2009).

Physical activity may be beneficial for people with AD and dementia. In 2004, Heyn et al

conducted a meta-analysis to determine whether exercise training is beneficial for people with

dementia and related cognitive impairment. The investigators concluded that exercise training is

beneficial for this group of people as it increases fitness, physical function, cognitive function,

and positive behavior. Teri et al (2003) conducted a randomized controlled trial to test the effect

of an exercise program combined with behavioral management on patients with AD. The results

showed an improvement in the patient's scores on the Physical Role Functioning (PRF) and

Cornell Depression Scale for Depression in Dementia (CDSD) compared to the control group,

suggesting improvements in both physical health and depression. Despite the current body of

evidence on the benefits of physical activity for people with dementia, Forebes et al (2008) concluded that there is insufficient evidence on the effectiveness of physical activity in improving cognition, function, behavior and depression in people with dementia due to the low number of trials that examined these outcomes.

The relationship between physical activity and cognitive function in older adults has been also studied. Higher levels of physical activities may moderate and modulate the decline in cognitive function associated with aging (Chodzko-Zajko, 1991; McDowell, Kerick, Santa Maria, & Hatfield, 2003), and among adults aged 70 to 75 years, higher levels of self-reported physical activity were correlated with lower decline in cognitive function measured using Mental Status Questionnaire (Pignatti, Rozzinni, & Trabucchi, 2002). In addition, physical activity had a protective role against cognitive decline in a sample of community dwelling elderly women (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001).

Arcoverde et al (2008) conducted a cross-sectional study to examine the association between physical activity, cognitive function, and performance in activities of daily living. The investigators concluded that physical and cognitive stimulation in patients with AD can decrease cognitive decline and limit functional impairment. These findings were re-examined in this retrospective study.

In summary, physical activity and exercise has been well studied in elderly population but not as well in the AD population. This literature review highlights the severe impact of AD upon the lives of patients, caregivers, as well as health care systems. Severe stages of AD are associated with disability and dependence, and the present study examined the early progression of disease symptoms with an assumption that this will provide professionals, patients, and families with information about the factors influencing declines in the patient's physical or

mental abilities, and with a more accurate description of the patient's present capabilities. This will help occupational therapists in designing effective interventions to manage some of the disease symptoms, to reduce the impact of the disease upon the life of patients and care givers, and to improve the quality of life of patients with AD. In addition, occupational therapists are becoming more involved in disease-prevention programs, and in promoting physical activities for older adults. Occupational therapy theories depend on the scholarly efforts of researchers to nurture the science of occupational therapy and to develop the clinical branch of this profession.

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