Leisure Activities and Risk of Dementia in Older Adults

By Aleksandra Sumic

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CERTIFICATE OF APPROVAL

This is to certify that the MPH thesis of

Aleksandra Sumic

has been approved

[redacted]
Professor in charge of thesis

[redacted]
Member

[redacted]
Member

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ABSTRACT

Context: As the elderly population expands, the number of dementia cases is rapidly increasing. Our understanding of dementia is still limited, and more research is needed to advance the current understanding of the risk factors. Since genetics do not sufficiently explain the disease, the idea of everyday activities (e.g. social and mental leisure activities and physical activities) as social risk factors for dementia has been increasingly drawing attention of researchers. These are modifiable risk factors that can be changed with significantly smaller costs compared to costs of medication and/or hospitalization. As people grow older, the frequency and the type of the leisure activities they participate in change. At the same time, some seniors experience significant change in cognitive function as well. Given these facts, the likely question to ask would be whether the frequency and the type of activities in which seniors engage could have an influence on their cognitive function. Despite the fact that the research in this area has significantly grown, no final judgment on the relationship of leisure activities and dementia has been made yet. Among other things, the disagreement stems from the inconsistent categorization of the activities, and often the categorizations seem to be based on definition of activity, not on specific hypothesis linking activity to the cognitive function.

Objective: To quantify the independent effects of physical activity (walking and exercise), social engagement and participation in leisure activities on cognitive function. The categorization of leisure activities in this study is based on their cognitive demand. Physical activity is assessed separately from mental and social leisure activities.

Study population: 212 older adults, 75 to 97 years of age, selected from the three prospective cohorts of older adults, the Oregon Brain Aging Study (OBAS), the Dementia Prevention Study (DPS) and the African American Dementia and Aging Project (AADAPt), a part of the Layton Center for Aging & Alzheimer's Research Center at OHSU.

Methods: Cognitively impaired and intact subjects are compared using ANOVA. Kaplan-Meier and Cox Proportional Hazard models are used to assess the relationship between the physical, social and cognitive activities at the study baseline and the time until cognitive impairment.

Conclusion: This study demonstrates a significant association between participation in 4 or more hours of exercise per week and reduced risk of cognitive impairment (HR 0.294; 95% CI 0.131, 0.660). The association remains even after adjustment for sex, education and health status. However, the study did not demonstrate significant association between participation in leisure activities and risk of cognitive impairment.

INTRODUCTION

Significance and Background information

The population of older adults is rapidly expanding in all developed nations. In the recent decades, their life expectancy has increased as well. In the United States alone, the populations of 90 year-olds is expected to reach 10 million by the year 2005, while over 25% of adults age 65 and above are expected to live to the age of 90.[1]

Reflecting this change in population demographics is the growing interest in a variety of research topics related to the health and well being of an older population. One of the biggest concerns older adults have is the preservation of cognitive function. This is perfectly understandable, considering that the ability to maintain independence and preserve quality of life depends largely on the preservation of cognitive function. In fact, for both the elderly and their families, the loss of cognitive function often represents one of the "most feared end-of-life tragedies."[2] As the elderly population expands, the number of dementia cases is rapidly increasing. Severe dementia is present in 6% of the population over 65 years of age, and moderate cognitive impairments in 10-15%. Of all severe dementia cases, 45% suffer from the Alzheimer's disease.[3] This destructive disease affects 50% of North Americans age 85 and above.[2] Although to different degrees, all forms of dementia take a devastating toll. Gradually increasing and irreversible loss of mental function ultimately leaves some of the patients completely incapable of independent functioning.

In addition, the health care costs, personal and national, related to cognitive diseases are another alarming aspect of this growing problem. In 1991, the direct cost of Alzheimer's disease was estimated at $20.6 billion, and indirect at $67.3 billion. The 1999 estimate of the yearly combined costs of dementia amounted to $100 billion.[3]

The field of research on cognitive diseases is constantly growing. Gradually, important discoveries are being made, and we seem closer to finding important answers than ever before. Unfortunately, our current understanding of dementia has not yet enabled us to develop effective therapies. Given the lack of effective therapies and extremely high costs of assisted living and hospitalization, it is easy to justify the need for interventions that would prevent, or delay, the onset of dementia and its devastating consequences. Despite the urgent need, adequate interventions are not in existence either. More research is needed to advance the current understanding of the risk factors for dementia. The development of successful interventions that would improve quality of life and enhance the independence of older adults may ultimately come as a result of better understanding of these factors.[4]

Pursuing this goal, researchers have been investigating a variety of potential risk factors, such as cardiovascular disease, brain inflammation and infraction, viruses, and oxidative damages from free radicals.[5] Genetic risk factors for dementia and Alzheimer's disease (AD) have been investigated as well. Although the presence of at least one copy of apolipoprotein E type 4 allele has been shown to increase the risk of AD,[6] it does not entirely explain the causes of the disease. In fact, it is currently believed that the majority of AD cases develop as a result of both environmental and genetic risk factors.[6] Looking for the answers beyond genetics, in recent years researchers have become increasingly

interested in identifying social risk factors for dementia. Currently, genetic inheritance is not modifiable, and it may be a long time before effective therapies become available to patients affected by dementia. On the other hand, social risk factors are modifiable factors that can be acted upon now, and consequently merit further investigation.

In the field of social epidemiology, the idea of everyday activities (e.g. social and mental leisure activities and physical activities) as social risk factors for dementia has been increasingly drawing the attention of researchers. To a certain extent, this interest has been sparked by the generally accepted idea that leading an active life helps to maintain cognitive abilities in older adults,[7] but even more so by the findings in the related areas of research in the fields of psychology, neurology, gerontology and psychiatry.

According to one of the aforementioned studies, participation of nursing home residents and elderly with dementia in temporary social and intellectual engagement interventions enhanced their cognition.[8] In addition, an association was demonstrated between participation in everyday activities and better performance on intelligence and memory tests.[9] Animal studies have also shown that leisure activities have a beneficial effect on cognition. Furthermore, it has been shown that maze-learning ability increased in rodents exposed to complex social and physical environments when compared to rodents exposed to simple environments.[8] Finally, long-term participation in cognitively stimulating activities has been found to impact neural structure in both rodents and humans.[10]

Sometimes thought of separately, and sometimes as a subcategory of leisure activities, the potential role of physical activity on cognitive function has also been an

important piece of this puzzle. Since physical activity has beneficial effects in many diseases including diabetes mellitus, osteoporosis, stroke, and coronary artery disease,[11] it is a natural inclusion in studies of leisure activities and cognition. Physical fitness interventions in older adults have also been found to benefit their memory and cognition.[11] When compared to anaerobic training (stretching and toning), aerobic training intervention (walking) increased performance on planning, scheduling, inhibition and working memory in older adults.[12] Furthermore, older adults who participated in aerobic exercise (walking and slow jogging) significantly improved their results on neuropsychological tests compared to the controls.[13] These findings, along with the well-established fact that healthy aging is associated with physical activity,[14] provide a strong rationale for the exploration of the relationship between physical activity and risk of cognitive decline.

Summary of the Current Research

As people grow older, the frequency and type of their leisure activities change. At the same time, some seniors experience a significant change in cognitive function as well. Given these facts, the likely question to ask is whether the frequency and the type of activities in which seniors engage influence their cognitive function. Indeed, this is not the novel idea in this area of research. In 1991, Salthouse proposed the disuse theory, arguing that cognitive processes and skills deteriorate as a consequence of disuse.[15] If this were true, the other researchers further argued, then it would be reasonable to expect that participation in leisure activities as exercise of cognitive skills would lead to stable, if not

improved, cognitive performance.[15] A number of studies have explored the role of participation in leisure activities as a potentially protective factor against cognitive decline in the elderly. Even though the body of research has significantly grown, the final judgment on the relationship between leisure activities, and physical activities, with cognitive function has not yet been made. Approaches to these questions are diverse, with differing measurements of the exposure and outcome of interest, among other things. Regardless, the results are intriguing and deserve attention. Following are two abridged summary tables of the current findings, describing the diversity and challenges encountered in this field.

Table 1. Review of the Cross-Sectional and Case-Control Studies of the Association Between Leisure Activities and Cognition

STUDY	N	LEISURE ACTIVITIES	OUTCOME OF INTEREST	RESULTS	COMMENTS
Christensen at al. (1996)[7]	858	Physical activity (sports, walking, gardening, cleaning), reading a paper, interests and hobbies, resting and napping, planned activities	Crystallized intelligence, fluid intelligence, memory and Mini Mental State Examination performance	Activity measures correlated significantly, but weakly with the crystallized intelligence, fluid intelligence, memory and MMSE (MANOVA correlation coefficients – 0.32 to –0.10)	Activity measures measured by composite scale combining physical activity, hobbies and interests Cross sectional study
Friedland at al. (2001)[16]	193 cases/358 controls	Passive, intellectual and physical activities during adulthood	Probable or possible Alzheimer's Disease (AD)	Control group was less active during adulthood than the case group activities of interest (OR 3.85, 95% CI 2.65-5.58, P < 0.001).	Age, gender, income and education controlled for AD diagnosis established by consensus conference using (NINCDS/ADRDA) criteria

STUDY	N	LEISURE ACTIVITIES	OUTCOME OF INTEREST	RESULTS	COMMENTS
Clarkson-Smith and Hartley (1989)[17]	62 cases/62controls	Physical exercise	Cognitive tasks performance (vocabulary, working memory, digit span, reaction time, reasoning)	Exercisers performed significantly better on measures of interest	Covariates: years of education and self-reported health

Table 2. Review of the Longitudinal Studies of the Association Between Leisure Activities and Cognition

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
Verghese at al. (2003)[18]	469	>75	Reading books or newspapers, writing for pleasure, doing crossword puzzles, playing board games or cards, participating in organized group discussions and physical activities (playing tennis or golf, swimming, bicycling, dancing, participating in group exercise, bowling, walking for	Alzheimer's Disease, vascular dementia, and mixed dementia	5.1 (median)	Association between leisure activities with reduced risk of AD (HR 0.93, 95%CI 0.88 to0.98), vascular dementia (HR 0.92, 95%CI 0.86 to 0.99), and mixed dementia (HR 0.87, 95%CI 0.78 to 0.93). No association between physical activity and the risk of dementia.	Sex, education, chronic medical illness, baseline cognitive status adjusted for. Leisure activities arbitrarily classified as cognitive or physical. Outcomes determined at case conference acc. to DSM-III and DSM-III-R manuals.

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
			exercise, climbing more than two flights of stairs, doing housework and babysitting)				
Fabriguole at al. (1995)[19]	2040	≥65	Sports or gymnastics, traveling, visits to friends or family, child care, participation in golden age clubs, reading, watching TV, playing parlor games, gardening, odd jobs, knitting.	Dementia	3	Traveling, odd jobs, knitting, and gardening associated with lower risk of dementia ($RR_{Traveling}$ 0.49, 95%CI 0.24-0.94; $RR_{Odd\ jobs\ or\ knitting}$ 0.46, 95%CI 0.26-0.85; $RR_{Gardening}$ 0.53, 95%CI = 0.28-0.99).	Baseline cognitive performance, age, physical capability and occupational activities adjusted for. Frequency of participation not recorded. Outcome assessed using NINCDS/ADRDA and DSM-III-R criteria.

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
Wilson at al. (2002)[20]	801	≥65	Viewing TV, listening to the radio, reading newspapers, reading magazines, reading books, playing games, going to museums and physical activities (walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding, and swimming or water exercise).	Alzheimer's Disease	4.5 (mean)	One-point increase in cognitive activity score associated with reduction in risk of AD (HR 0.67, 95% CI 0.49, 0.92). Physical activity not related to the risk of AD	Physical and leisure activities measured using composite scales. Age, sex and education controlled for. Outcome diagnosed by a board-certified neurologist using NINCDS/ADRDA criteria.
Scarmeas at al.	1772	≥65	Knitting, music or other	Dementia	2.9 (mean)	Associated with	Outcome diagnosed at the

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
(2001)[21]			hobby, walking for pleasure or excursion, visiting friends or relatives, being visited by friends or relatives, physical conditioning, going to movies, restaurants or sporting events, reading magazines, newspapers or books, watching TV or listening to the radio, doing volunteer community work, plating			reduced risk of incident dementia: reading magazines or newspapers (RR 0.49; 95%CI 0.35 to 0.68), visiting friends or relatives (RR 0.60; 95%CI 0.45 to 0.80), going out to movies or restaurants (RR 0.62; 95%CI 0.44 to 0.86), and walking for pleasure or going for an excursion (RR 0.73, 95%CI 0.55	consensus conference using NINCDS/ADRDA criteria. Aggregate score used for all of the activities. Age, race, education and occupation controlled for.

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
			cards or bingo, going to a club, going to classes, going to the church, synagogue or temple.			to 0.98). Leisure items also grouped into intellectual, social and physical. All three remained significant.	
Wang at al. (2002)[22]	776	≥75	Mental (reading books or newspapers, writing, studying, painting, drawing, doing crosswords puzzles), social (attending the theater, concerts, or art exhibitions, traveling,	Dementia	6.4 (mean)	Engagement in mental, social, and productive activities inversely related to dementia incidence. Adjusted RR_{mental} 0.54 (95%CI 0.34-0.87), RR_{social} 0.58 (95%CI 0.37-0.91), and	Outcome diagnosed by specialists according to DSM-III-R. Age, sex, education, comorbidity, depression, cognitive function and physical functioning controlled for.

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
			playing games, participating in social groups), physical (swimming, walking, gymnastics), productive (gardening, cooking, housekeeping, working, volunteering, sewing, knitting, weaving), and recreational (watching TV or listening to the radio).			$RR_{productive}$ 0.58 (95%CI 0.0.38-0.91).	
Aartsen at al. (2002)[4]	2076	55-85	Social activities (visiting church, visiting	Tests of cognitive functioning: immediate recall,	6	No activity associated with cognitive functioning.	Age, gender, education and health controlled for.

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
			neighborhood associations, visiting meetings of associations of older adults), experiential activities (going to the forest, dunes, zoo, or entertainment park, visiting museum, theater or cinema, visiting café or restaurant), and developmental activities (following an educational course, doing outdoors sports).	learning, fluid intelligence, information processing speed and Mini Mental State Examination.			
Yaffe at al.	5925	≥65	Physical	Cognitive	7.5	Women in	Age, education,

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
(2001)[23]			activity (self-reported blocks walked per week and total kilocalories expended per week in recreation, blocks walked, and stairs climbed)	decline (defined as a 3-point decrease on Mini Mental State Examination test).	(mean)	the highest quartile less likely then women in the lowest quartile to develop cognitive decline ($OR_{blocks\ walked}$ 0.66, 95% CI 0.54-0.82; $OR_{total\ kilocalories}$ 0.74, 95% CI 0.60-0.90)	comorbidity, smoking, estrogen use and functional limitations controlled for.
Laurin at al. (2001)[11]	4615	≥65	Three levels of physical activity: engagement 3 or more times per week at an intensity greater than walking, engagement 3	Cognitive impairment and dementia	5 (mean)	High levels of physical activity associated with reduced risk of cognitive impairment (OR 0.58; 95%CI	Diagnosis made by the physician and neuropsychologist in a consensus conference according to DSM-III-R. Age, sex, and

Study	N	Age at baseline (years)	Leisure Activities	Outcome of interest	Follow-up (years)	Results	Comments
			or more times per week at an intensity equal to walking, and no regular exercise.			0.41-0.83), Alzheimer's disease (OR 0.50; 95%CI 0.28-0.90), and dementia of any type (OR 0.63: 95%CI 0.40-0.98).	education adjusted for.

These summary tables are not exhaustive, but they capture most of the extant findings and lines of thought on impact of leisure activities on dementia in older adults. Briefly, a number of studies demonstrated an association of participation in leisure and physical activities with the reduced risk of dementia, but several negative findings have been published as well.

Inconsistencies in the Current Research

Even if they agree on their conclusions, these studies are marked by great diversity in study design and quality.

Some of the earlier studies were cross-sectional. In this type of design both participation in leisure activities and cognitive status are assessed at the same point in time, consequently restricting conclusions on causation. In particular, the cross-sectional design cannot answer the question whether cognitive impairment causes older adults to participate less in leisure activities, or whether they develop cognitive impairment as a consequence of the insufficient participation. Only prospective designs can appropriately address this concern.

On the other hand, prospective studies have inconsistently controlled for potential confounding variables such as age, gender, socioeconomic status, education, race, functional limitations, comorbid conditions, and depression. Lack of control for important confounders in some research could result in artificial associations or lack thereof. Also, inconsistency makes comparisons of some of the studies very difficult.

Most heterogeneity in these studies is found in the definition and categorization of the leisure activities. Different studies measured different types of leisure activities. Some of the studies report only what type of activity subjects engage in but do not assess the frequency of participation. In addition, mental and physical activities were frequently combined into one category.[24] If the leisure activities were at all categorized, the reasoning behind a particular categorization was rarely explained. Often the categorizations seemed to be based on definition of activity, not on a specific hypothesis linking the activity to the cognitive function.

Designing the Adequate Leisure Activities Categorization

A number of studies demonstrated an association between participation in leisure activities and decreased risk of cognitive decline. Not all of those activities require the same cognitive effort. For example, Bassuk and colleagues remark that the level of cognitive involvement needed for intellectual discussion or watching TV could differ from the cognitive involvement needed for visual contact with a friend.[8] Given this possibility and the premise that participation in leisure activities decreases the risk of cognitive decline, it is reasonable to ask whether different activities impact cognition in different way.[4]

Some studies addressed this question in varying ways and degrees, but most often the categorization was not hypothesis driven or supported by any specific theory.

One attempt to take into account the cognitive demand of the leisure activities is the categorization by Schooler.[25] He classifies all activities into two major groups. The first

category consists of less cognitively demanding "Passive Life Style" activities and includes social activities (visiting friends, attending a party), self-maintenance (preparing a meal or shopping), and passive information processing (listening to the radio or watching a sporting event). The second category consists of more cognitively demanding "Active Life Style" activities and includes physical activities (walking or jogging), integrative information processing (driving a car or playing an instrument), and novel information processing (learning a language or playing bridge).[9, 25]

This categorization is based on his argument that cognitive performance in later life might be impacted by the type and frequency of everyday activities in which older adults participate.[9, 25] In addition, Schooler suggests that mechanisms that maintain cognitive stability might be preserved by participation in cognitively demanding activities.[9, 25]

An example of Schooler's categorization at work can be found in the research of Hultsch. Relying on this categorization, in one of his studies he examined the relationship between activity life style and performance on a range of cognitive tests. His research indicates that an active life style is associated with cognitive performance[9] but his study was correlational, hence limiting conclusions on causation.

Although this categorization recognizes the cognitive demand of different leisure activities, it is important to note that it also combines mental and physical activities in the Active Life Style category.

The Current Study

Using unique longitudinal data collected as part of the Layton Center for Aging & Alzheimer's Research Center, at OHSU, this study will explore the relationship between leisure activities and risk of dementia in older adults. Aforementioned research shortcomings will be addressed by using a prospective cohort of older adults, controlling for important confounding variables, and by applying a design that classifies leisure activities in a way that recognizes their cognitive demand and addresses the questions of the impact of physical activity and mental activity separately. Also, the type and frequency of leisure activities which this study explores come from a questionnaire specifically designed with the older population in mind. The units which measure the frequency of participation in leisure activities in this study will be meaningful to the population in question, as well as practical and applicable in development of medical recommendations and prevention strategies. Cognitive status of the participants was assessed by clinical evaluation.

Specific Aims

This study has two specific aims.

First, the study will quantify the independent effects of physical activity on cognitive function. Two specific hypotheses tested under this aim are:

1) Greater baseline walking is associated with reduced risk of cognitive decline.

2) Greater baseline participation in physical exercise is associated with a reduced risk of cognitive decline.

The second specific aim is to quantify the independent effects of social engagement and participation in leisure activities on cognitive function. The specific hypothesis tested under this aim is:

Leading a cognitively active life style at study baseline (engagement in cognitively more demanding social and leisure activities), as opposed to a cognitively passive life style (engagement in less cognitively demanding social and leisure activities), is associated with a reduced risk of cognitive decline.

METHODS

Parent Studies

The Oregon Brain Aging Study (OBAS) has been previously described in detail elsewhere.[2, 26-30] Briefly, the OBAS was begun in 1989 at, what is today known as, The Layton Center for Aging & Alzheimer's Research, at Oregon Health and Sciences University, as a longitudinal study of the effects of aging on the central nervous system in the optimally healthy elderly of 65 years of age and older.[2] The participants were identified and recruited from retirement homes, senior citizens' organizations and public relation activities.[28] The principal language for all the recruited volunteers was English, and they were required to have adequate hearing and be able to read letters 4 mm tall.[28] All were community dwelling, functionally independent older adults.[28] The study enrolled the healthiest elderly, therefore they were cognitively healthy and free of any

conditions that might affect cognition (see Appendix for exclusion criteria). After enrollment, all the participants were assessed biannually for medical history, functional independence (measured by Instrumental Activities of Daily Living Scale from the Older American Resources and Services), cognition (Mini Mental State Examination and Clinical Dementia Rating Scale), and annually for a full physical examination, neurological, neuropsychological and brain MRI examinations.[2] Blood samples were collected, DNA was extracted and Apolipoprotein E (apoE) genotypes were obtained. Upon death, brain autopsies for neuropathological analysis were performed.[2] All subjects gave informed consent.[27]

The Dementia Prevention Study (DPS), a project of the Oregon Center for Complementary and Alternative Medicine in Neurological Disorders, is a five year pilot study of the effect of standardized ginkgo biloba extract on cognitive decline in people age 85 years or older. One hundred thirty three cognitively unimpaired elderly subjects of average physical health were enrolled in this randomized, placebo-controlled, double blinded study. They are being followed to detect conversion to mild cognitive impairment (also known as 'questionable dementia'), a precursor to dementia. The study focuses on the oldest old because they are at particularly high risk for developing MCI. Besides investigating the effect of gingko biloba extract on cognitive impairment, perhaps more importantly this study provides a unique opportunity to examine recruitment and participation of oldest old in a clinical trial. Participants were recruited primarily through mass mailings to age-eligible individuals in the greater Portland area, and also through observational studies already taking place in the OHSU Aging & Alzheimer's Disease

Center. The screening process included a medical record review and assessments administered on the telephone and at a home visit. Given the rarity of optimally healthy oldest old, this project targeted oldest old who were cognitively and functionally intact, but not necessarily without comorbidities. A detailed inclusion criteria list can be found in the Appendix. Neuropsychological assessments are completed every six months at the participants' homes. Eighteen months into the study, the study did not have significant problems with attrition and compliance.[31]

The African American Dementia and Aging Project (AADAPt) cohort was designed with the goal of establishing a group of self-reported African-Americans aged 65 years or older, residing in the Portland metropolitan area. In addition the inclusion criteria required that the participants are able to walk, and have vision, hearing and language abilities adequate for the understanding of the consent form and completion of study assessments. Also, the participants should have available collateral historian, be willing to sign informed consent and have no evidence of dementia at entry. The details on inclusion and exclusion criteria for this cohort can be found in the Appendix. The study is designed to identify the incidence and potential risk factors of cognitive decline and/or dementia in this population, and to identify factors associated with the recruitment and retention of such a cohort. This study is specifically designed to gather baseline physical, cognitive, psychosocial, and environmental data on factors, which may be associated with incident cognitive decline leading to dementia in African-Americans, and to generate hypotheses regarding such factors. The participants received a brief telephone

or community-based follow-up, and full clinical assessments at OHSU every 12 months. There is no intervention component to this study.[32]

Study Sample

In this study, a secondary data analysis using data collected on the OBAS, DPS and AADAPt cohorts as part of the Layton Center for Aging & Alzheimer's Research Center, at OHSU, will be used to test the hypotheses. The study sample consisted of 212 older adults. Every six months their medical history was updated, and functional independence and cognitive function were tested. Every year all participants underwent a full physical examination and a battery of neurological and neuropsychological tests. The baseline for this study is defined as the first time the participants responded to the Personal and Family History Form and provided information about the social activities, hobbies, interests, as well as the physical activities. Subjects selected for the current study were cognitively intact, functionally independent, and depression free seniors who live independently and have been followed for at least one year.

Measurement of Leisure and Physical Activities

Leisure Activities

In the baseline questionnaire, the participants reported their social activities, hobbies, and interests. They provided information on participation in 17 activities (Table

3), and the frequency of the participation as "daily", "weekly", "yearly", and "rarely or never".

To test the hypothesis that leading a cognitively active life style at baseline (engagement in cognitively more demanding social and leisure activities), as opposed to a cognitively passive life style (engagement in less cognitively demanding social and leisure activities), is associated with reduced risk of cognitive decline, the OBAS social and leisure activities were classified according to their cognitive demand following the modified Schooler[25] and Hultsch[9] categorization:

1) Social Activities

Owning and caring for pet

Having visitors

Visiting others at their homes

Going out to eat

Attending a club or group meeting

Attending church or synagogue services

2) Passive Information Processing

Listening to a TV or radio news program

Listening to music

Watching a favorite TV or sports program

Watching a movie

3) Integrative Information Processing

Traveling out of town

Spending time at a hobby or game

4) Novel Information Processing

Reading a newspaper

Reading an entire book

Following finances or investments

Taking a class

Using a computer

Following the categorization further, the four categories were then classified into two major groups that will be used as final categories for the analysis:

1) Active Life Style – consisting of integrative information processing and novel information processing.

2) Passive Life Style – consisting of social activities and passive information processing.

The scoring scheme for the evaluation of participation in different activities was adopted from Verghese,[18] and subsequently modified to better reflect the specifics of the activities available in this study. The Verghese scale assigns one point to participation in one activity for one day per week. The goal was to develop a practical scale for use in public health studies and recommendations, which is easily understood by clinicians and older adults alike.[18]

For each activity, the modified Verghese scale assigns seven points for daily participation, one point for weekly participation, 0.5 points for monthly participation, and 0 points for yearly or rarely participation. The modified scale closely resembles the original scale, but accommodates the fact that some of the activities in this study are more

commonly occurring on monthly basis (such as traveling out of town or attending some group meetings). Therefore, it recognizes participation in those activities by assigning half of a point to them, where the original scale assigns none.

Variable 'Active Score' was created as a sum of all points a participant accrued for participation in cognitively active activities (using a computer, taking a class, following finances or investments, reading an entire book, reading a newspaper, spending time at a hobby or game, traveling out of town). Variable 'Passive Score' was created as a sum of all points a participant accrued for participation in cognitively passive activities (watching a movie, watching a favorite TV or sports program, listening to music, listening to a TV or radio news program, attending church or synagogue services, attending a club or group meeting, going out to eat, visiting others at their homes, having visitors, owning and caring for pet). Since participation in cognitively active leisure activities does not exclude participation in cognitively passive activities, and vice versa, the scheme had to be devised that would allow for the comparison of the two groups. This was accomplished by splitting both groups along the median to create high (above median) and low (below median) groups. This split was used to create 4 possible combinations of the activities: low active/ low passive, low active/ high passive, high active/ low passive, high active/ high passive groups that will eventually be compared in the analysis.

In addition, the variable 'Total Activity' was created as a sum of all points that a participant accrued for participation in both cognitively active and passive activities.

Physical activities

Information about participation in physical activities was also reported in the baseline questionnaire. The participants were asked to provide information on how many city blocks they walk daily (12 blocks = 1 mile), how many hours per week they participate in light physical exercise (walking, biking, dancing, golfing, gardening) and strenuous physical exercise (running, jogging, swimming, hunting, wood splitting, working with livestock or other strenuous farm work, skiing, tennis, hiking, strenuous yard work or home maintenance).

The variable 'Exercise' was created as the total number of hours each participant spent in light and strenuous physical exercise together.

As the name suggests, the variable 'Blocks walked' consists of the reported numbers of blocks walked per week

In addition to their continuous forms, both 'Exercise' and 'Blocks walked' variables were further categorized using a quartile split.

Assessment of Cognitive Function

Cognitive Impairment

Cognitive decline was measured using the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating Scale (CDR).

The MMSE is a short quantitative assessment of cognitive status with the maximum score of 30.[2, 33] This clinical instrument is widely used for fast detection of

cognitive impairment and assessment of its severity. It is also used to monitor cognitive changes over time.[33]

The CDR is a clinical instrument for staging of dementia. Information on six areas of cognitive and functional performance is obtained and assessed in a semi-structured interview with a subject. The score of 0 is assigned if no impairment is detected, 0.5 for very mild or questionable dementia, and 1-3 for different severity levels of definite dementia. In addition, a reliable collateral informant, such as family member or friend, is interviewed to verify the information reported by the subject in the interview. The information reported by the collateral informant is also assessed and assigned the scores of 0.5-3.[2, 34]

Cognitive decline is defined as repeated abnormal scores on the MMSE (<24) or the CDR (>=0.5) on two consecutive assessments.[2] This definition, developed by the Layton Center for Aging & Alzheimer's Research Center at OHSU, relies on two consecutive assessments rather than one to account for the possibility of one abnormal score resulting from the reasons unrelated to the cognitive status (e.g. bad day, personal reasons etc).

The age of onset will be defined as the age at the time the participant received the first of the two consecutive abnormal scores on the MMSE or the CDR.

Clinical Dementia Rating Scale

The result of CDR assessment is reported as two different scores. First score, the CDR score, represents the points a patient received on the assessment. The second score,

the collateral CDR score, represents the points received for the assessment of the information provided by the collateral informant.

For the analysis in this study, a Master CDR score was created as a greater of the participants' CDR and collateral informant's CDR score.

Current Diagnosis and Age at Onset

Included in the analysis were all participants for whom the outcome information was available. This information was contained in the variables called 'Current Diagnosis' and 'Age at Onset'. For those who developed cognitive impairment, the 'Current Diagnosis' consists of the particular dementia diagnosis, and the 'Age at Onset' provided the age when the subject first scored 0.5 or more on Clinical Dementia Rating Scale (CDR), or less than 24 on Mini Mental State Examination (MMSE).

The subset of the participants who had 'questionable dementia' (QUESTDEM) status for their current diagnosis, as well as those who had 'normal' current diagnosis but extant age at onset, had to be additionally assessed for the verification of their 'Current Diagnosis' status.

Two possible scenarios during assessment can lead to the 'questionable dementia' diagnosis. In the first scenario, the very first time a subject scores <24 on the MMSE or >= 0.5 on the CDR, he/she converts to the 'questionable dementia' status. If she/he scores in the abnormal range on the next assessment as well, the diagnosis changes to 'cognitively impaired'. If, on the other hand, the subject performs within normal range

the 'questionable dementia' diagnosis remains. If following this assessment the subject scores within the normal range again, the diagnosis reverts back to 'normal'. Important to note is that regardless of the current diagnosis status, had the conversion to questionable dementia ever occurred, the 'Age of Onset' variable will always show the age of the first conversion to 'questionable dementia'.

In the second scenario, a patient diagnosed with 'cognitive decline' due to two consecutive scores of 0.5 or more on Clinical Dementia Rating Scale (CDR) or <24 on Mini Mental State Examination (MMSE) can convert to 'questionable dementia' status if she/he scores within the normal range again, and back to 'normal' if he/she scores within the normal range two consecutive times after being diagnosed as cognitively impaired.

Since this study defines the age at onset as the age at the time the participant received the first of the two consecutive abnormal scores on the MMSE or the CDR, regardless of any previous or future conversions for the better or for the worse, all the participants with 'questionable dementia' status and/or extant age at onset had to be re-evaluated. Their assessment histories were obtained, the age at onset and the current diagnosis confirmed and updated as needed.

Status

Status variable was created to allow categorization of all participants according to their current diagnosis and age at onset into cognitively impaired or cognitively intact . For the purposes of the survival analysis, the cognitively intact are considered 'censored

observations' and were assigned code 0. The cognitively impaired who developed the event of interest are considered as 'failures' and were assigned code 1.

Follow-up

The length of the time that each of the participants was followed had to be made available for the analysis. This was accomplished by creating the 'Follow-up' variable. For the subjects with cognitive impairment status, this variable was created as difference between the age at the onset of the cognitive decline and their age at the study baseline (evaluation age). For the cognitively intact subjects this variable was created as the difference between their age at last evaluation and age at the study baseline (evaluation age).

Assessment of Covariates

Previous research[2, 4-6, 8, 10, 16, 18, 21, 22, 26, 27, 30, 35] has identified certain covariates as important confounders of the relationship of physical and leisure activities with cognitive function. Consequently, the selection of the important covariates was taken into consideration in this study as well.

Age

The participant's age at the study baseline was reported in the 'Evaluation Age' variable. Remember that the baseline for this study is defined as the first time the participants responded to the Personal and Family History Form and provided information about the social activities, hobbies, interests, as well as the physical activities.

It is important to note the difference between this variable and variable 'Age at Entry' which refers to the participant's age at the entry into one of the Layton Center's cohorts. For some participants this happened before the current study baseline, while for others the two might coincide.

Finally, variable 'Age at Last Evaluation' refers to the age when the participant was last evaluated.

Sex

The variable Sex was coded 1 for males and 0 for females.

Education

The years of education were reported in the 'Education' variable.

Socioeconomic Status

Socioeconomic status was reported as the Hollingshead Social Status score. This four factor index estimates the social status of an individual based on education, occupation, sex and marital status.[36]

Race

The variable Race was recoded as white, black, and other.

Place of Residence

Participants' place of residence was included as one of four categories: home/apartment, retirement community, assisted living, nursing home.

Living Arrangement

Since previous research has identified living alone and being single as strong risk factors for dementia, the information on living arrangements was included into analysis in this study as well.[35] The living arrangement variable was recoded as 'alone' versus 'not alone'.

Apolipoprotein (APOE) Genotype

Apolipoprotein (APOE) genotype status was recoded to answer the question whether the participant possesses at least one or more copies of the $\in 4$ allele. The new dichotomous variable 'APOEnew1' was created so that 0 represents 'no', and 1 represents 'yes'.

Cohort

The cohort membership was originally included as 3 categories: OBAS, DPS, and AADAPt. For the inclusion into analysis, this variable had to be further recoded as an indicator variable. Using AADAPt as a referent cohort category, the OBAS indicator variable was assigned value of 1 for OBAS cohort members, and 0 for DPS. The DPS indicator variable was assigned a value of 1 for DPS cohort members, and 0 for OBAS.

IADL

The older Americans Resource Scale Instrumental Activities of Daily Living (IADL) refers to the activities associated with independent living, and includes preparing meals, managing money, shopping for groceries or personal items, performing light or heavy housework, and using a telephone.[37] The ability of older adults to perform these activities is graded as independent, dependent or assistance needed, and is evaluated to assess their functional capabilities.[38] In this study, functional independence was defined by the IADL score of 12 or less.[2]

Gait

Gait was recorded as the 'number of steps per second'. It was determined from the number of steps and the time taken to walk 30 ft (average of three trials).[29]

Depression

Depression was measured using the 4 different scales for different participants (Geriatric Depression Scale (GDS), Cornell Depression Scale (CORNELL) and two versions of the Center for Epidemiologic Studies Short Depression Scale (CES-D 10)).

Consequently, a master depression variable that would allow the results from the different scales to be combined into one new variable had to be created. Essentially, the master depression variable is a non-numeric combination of different depression scales that were available for the different subjects. In this variable the participants are simply categorized as either depressed or non-depressed. Subjects with values of >= 11 on the Cornell scale, >= 12 on GDS scale, >= 10 on CESD10 scale, or >= 10 on CESDWK scale were categorized as depressed, otherwise as not depressed.[2, 39]

Neuropsychological Tests

Neurlogical changes occur with aging, even though not all of them can be attributed to the disease process. Howieson at al. point out that there is a difference between age-related cognitive decline and dementia in the oldest old. For example, it has been

determined that verbal memory declines in the preclinical stage of Alzheimer's disease.[27] In addition, performance on Logical Memory II test was identified as the predictor of the onset of questionable dementia.[30] Because of their relevance, information on the following neuropsychological tests was also obtained at a baseline and included in the analysis:

1) Boston Naming Test and Boston Naming Test abbreviated version

This test measures the ability to name line drawing of familiar objects.[28]

2) Visual Reproduction

Recall of geometric designs is obtained on this test from the WMS-R by having subjects draw each design immediately after it is presented for 10 seconds (Visual Reproduction I) and after a 30-minute delay with intervening tasks (Visual Reproduction II).[28]

3) Word List Memory

The word memory test comes from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery. The test consists of an immediate recall of 10 words which are read to a subject (Acquisition score). Following a short break with distraction , delayed recall of the same words (Delayed Recall score) is tested.[28]

4) Verbal Fluency

Subjects were asked to say aloud as many animals or animals, fruits and vegetables as they could within given time.[7]

5) Logical Memory

The scores on the Logical Memory tests from the Wechsler Memory Scale consist of two tests, Logical Memory I (immediate recall of the two short stories, A and B) and Logical Memory II (recall of the two short stories, A and B, after a 30 minutes delay).[28] Two different versions of these tests were used during the course of data collection (WMS-R and WMS-III). The only section that overlaps in two versions is the story A, so only data from this story could be used for analysis.[26] Thus, Logical Memory I (LMI) variable was created, and it consists of the scores for the story A that were available for the participants, regardless of the version of the test. Another variable that was created is the Logical Memory II (LMII), and represents the scores available for the participants for the recall of the story A after the 30-minute delay, regardless of the version of the test.

Modified Cumulative Illness Rating Scale

Health status can significantly influence the ability of an older adult to walk, to exercise, or to choose the type and the extent of leisure activities in which they engage. Due to its role as an important confounder, the health status of the participants had to be controlled for in the analysis. For the cohorts used in this study, the health status was available in the form of Modified Cumulative Illness Rating Scale (MCIRS). Lower scores on this scale represent better overall health (see Appendix). The Modified Cumulative Illness Rating Scale (MCIRS) scores were missing for a subset of the study sample (Table 4).

Table 4. Modified Cumulative Illness Rating Scale (MCIRS) Summary

Cohort	N Available	N Missing
AADAPt	15	0
DPS	83	2
OBAS	36	76

The missing MCIRS data problem was addressed by using multiple imputation, which is described in the data analysis section.

Data Analysis

Descriptive statistics (mean, standard deviation, median, maximum, minimum, number of missing values) were obtained on all continuous variables to detect important trends in the data. Percentages of subjects belonging to each group of every categorical variable were obtained as well.

Using the one-way ANOVA, the three cohorts were compared on evaluation age, sex, education, socioeconomic status, duration of follow-up, and performance on the baseline Mini Mental State Examination (MMSE) to better inform the decision to pool them into one study sample.

The exclusion criteria were applied to arrive at the final version of the data set for the analysis. All subjects who were less than 75 years of age, demented (MMSE <24 and/or CDR >= 0.5), depressed, lived in foster or nursing homes, or had Independent Activities of Daily Living (IADL) scores greater than 12 at the study baseline were excluded from the final analysis. Participants who have been followed for less than one year were excluded as well.

Using the Wilcoxon test, cognitively impaired and cognitively intact participants were compared on the mean evaluation age, education, socioeconomic status, duration of follow-up, baseline IADL scores, and baseline MMSE scores. In addition, the difference in the proportion of females and proportion of subjects with at least one Apo E allele type 4 between cognitively impaired and cognitively intact was compared using the binomial test. Using the Chi-square test, the relationship between cognitive status and living arrangement (alone vs. not alone) was examined. Finally, the baseline performance on neuropsychological tests between cognitively impaired and cognitively intact was compared using the t-test.

The mean evaluation age, years of education, socioeconomic status, duration of follow-up, age at onset, baseline MMSE score, baseline IADL scores, and performance on the neuropsychological tests were compared by quartile of blocks walked, quartiles of hours exercised, quartiles of total leisure activity score, and by leisure activity groups and differences tested using one-way ANOVA. Living arrangement (alone vs. not alone) and sex were compared using Chi-square tests. In addition, the racial composition of the quartiles above was obtained.

The frequency of cognitive decline by quartiles of hours exercised and blocks walked was compared using the Chi-square tests.

Self-reported information on participation in leisure and physical activities was statistically validated. Pearson's correlation coefficient was obtained for the correlation of light exercise with walking, of gait with walking, and of gait with light exercise.

Preliminary Analysis

In the preliminary analyses, survival curves for the different groups for all relevant variables were estimated using the Kaplan-Meier method, and the differences were tested using the log-rank statistic. For this purpose, the continuous variables of interest were recoded into categorical variables in the most meaningful way (e.g. median or quartile split) (Table 5).

The hypothesis tested by the Log-Rank test is that there is no overall difference between the survival curves for the different groups of the variable in question. Any p value less than 0.15 was considered statistically significant in the preliminary analysis.

In addition to Kaplan-Meier analysis, the univariate Cox regression was also carried out on all continuous variables (Blocks walked, Exercise, Total Activity, MMSE, SES, Education, Evaluation Age, Word Acquisition, Delayed Recall, Animals, IADL, LMI, LMII, Boston Abbreviated test, Steps per Second). Since most of these variables were to be included in the final model building in their continuous form, this was an important addition in the preparation for the model building.

Variables identified as significant in the preliminary analysis along with important confounding variables were used to develop three different multivariate Cox Proportional Hazards models.

Building Cox Proportional Hazards Models

1) Cox Proportional Hazards Model I

The first model was developed using all study participants regardless of the availability of their Modified Cumulative Illness Rating Scale (MCIRS) scores. The variable MCIRS itself was not included in this model building.

Variables that were significant at 0.15 level in the Kaplan-Meier analysis and univariate Cox regression, except for the MCIRS variable, were entered into the model together. Among others, both ACTIVITY0 and Total Activity variables were identified as candidates for the inclusion into the model building. Although they were constructed differently, both of these variables refer to the same exposure – the leisure activities. Consequently they could not be used together in the model. As a result, one model was developed using the categorical ACTIVITY0 variable along with all other significant variables. The other model was developed using the continuous Total Activity variable instead. The same variables remained significant in both of these large models, and were retained for the next steps in the model building process.

All the possible interactions were evaluated one at a time. The interaction terms for the OBAS indicator variable were also checked for significance to further elucidate a possible cohort influence.

Finally, because of the previous research and the differences observed among the three cohorts, the important confounding variables, sex and education, were included in the model.

The proportional hazards assumption was examined graphically. For every variable in the model Kaplan-Meier survival curves, hazard functions, and log-log (-ln-ln) survival curves were plotted.

2) Cox Proportional Hazards Model II

The second proportional hazards model was a complete case analysis of the data, meaning that the model was fitted using only those participants for whom the MCIRS information was available. This model serves to elucidate if the subset of subjects for whom MCIRS scores were available differs in any systematic way from the participants for whom MCIRS information was not available, therefore serving to further validate the first Cox model.

The model was fitted starting with the same selection of variables used in the building of the Cox I model. Significant variables were retained in the model and the interactions tested one at a time. As before, interaction terms for the OBAS indicator variable were evaluated to assess a potential cohort influence. Finally, the important confounding variables, sex and education, were included into the model.

3) Cox Proportional Hazards Model III

The third model was developed to adequately address the problem of missing data.

3.1) Dealing With the MCIRS Missing Data in the Current Study

Multiple imputation was the method of choice to address the problem of the missing data in this study. It was performed using IVEware, a SAS callable software

application.[40] Among other things, this application can perform single or multiple imputation of missing values using the Sequential Regression Imputation Method.[40] The multiple imputation process consisted of three phases:

3.2) Phase I: Linear Regression Model for The Multiple Imputation – Selecting the Best Model for Predicting the Missing MCIRS Values from the Other Variables in the Data Set

First, using the complete data set, which includes only participants for whom MCIRS information was available, a linear regression model was developed by using MCIRS as the outcome variable, and a selection of relevant variables from the data set as covariates.

Upon the close examination of data, variables that had no relevance for the model and those which had a large number of missing values were excluded from the analysis. Using correlation coefficient greater than 0.8 as a cutoff point, the remaining variables were further examined for correlation among themselves and with MCIRS. Where applicable, only one of the two highly correlated variables was included in the further analysis. Simple linear regression (SLR) was conducted on each of the variables left available after the elimination step above. All variables significant at 0.25 level were retained and used to develop the multiple linear regression model. Since the purpose of this model was not description but prediction, the model with the largest adjusted R^2 value was selected, and examined for gross departures from normality using the normal probability plot and the plot of studentized residuals against predicted values.

3.3) Phase II: Multiple Imputed Data Sets

Based on the multiple regression model described above and fitting it to the participants for whom MCIRS information was not originally available, the Impute Module of the IVEware[40] application was used to generate five imputed data sets. Each set now contained imputed MCIRS values for the participants who originally did not have these scores reported.

3.4) Phase III: Cox Proportional Hazards Model III

The five imputed MCIRS variables generated in the step 3.3 were merged with the original data set one at a time to produce five different versions of the original data set. These five newly generated data sets were then analyzed using the Regress Module of the IVEware[40] to arrive at one final Cox model. The IVEware[40] repeats the same Cox regression analysis on each of the five data sets. Then, it combines the point estimates and variances from the five analyses to arrive at the point estimate and the variance for the final model. The interactions were evaluated and the important confounders, sex and education, were added to the model.

RESULTS

Study Sample Characteristics

The original study population consisted of 345 participants, 190 of whom were contributed by the OBAS cohort, 96 by the DPS cohort and 59 by the AADAPt cohort.

Of those 345 participants, 98 were below 75 years of age, 2 did not live independently, 5 had a baseline MMSE < 24, 10 had CDR (master) greater or equal to 0.5, 3 were depressed, 3 had depression status missing, 3 had IADL greater than 12, 2 had IADL missing, and 60 had been followed for less than one year. Also, 7 participants were missing evaluation diagnosis information and 1 was missing outcome information. Note that these categories are not exclusive, and that the same participants could belong to more than one single category. Upon exclusion of the 133 participants who did not meet the study criteria, the final study sample consisted of 212 participants, 112 of whom were from OBAS, 85 from DPS and 15 from AADAPt.

Out of 212 final study participants, 160 remained cognitively intact (23 dead, 137 alive, 0 lost to follow-up), while 52 developed cognitive decline (Table 6). The mean age of onset for cognitive impairment was 89.98 years of age.

The comprehensive list of all variables in the data set can be found in the Table 5. The descriptive statistics for all variables relevant for the analysis were obtained and examined for unusual observations (Tables 3 and 7). It was noted that variables MCIRS (Modified Cumulative Illness Rating Scale), Visual Reproduction 1, Visual Reproduction 2, Verbal Fluency – Animals Fruits Vegetables, and Boston Naming Test have a high number of missing values. This was the result of the decision by the Layton Center for Aging & Alzheimer's Research to stop assessing participants on these particular tests. The variable Exercise had a wide range, with the maximum value of 120. The minimum value for follow-up was 1 year. The low minimum can be attributed to the influence of

the relatively recently formed AADAPt cohort (the follow-up range for this cohort is only 1 - 2.6 years). The variable MCIRS was missing for 78 participants, mostly OBAS cohort members (Table 4).

The comparison of the three cohorts revealed that they did differ statistically with respect to sex, but did differ with respect to socioeconomic status, education, evaluation age, and follow-up. Most importantly, they were not statistically different in their baseline MMSE scores (Table 8). This key similarity supported the decision to combine the cohorts into one study sample, and to statistically control for the other relevant variables in the analysis. The results of the model building, discussed shortly, further justified this decision.

The racial composition of the three cohorts was not the same either. The AADAPt cohort is an entirely African-American cohort, while OBAS and DPS consist primarily of the Caucasians (Table 8). An extremely small number of non-white participants did not allow for any meaningful statistical comparisons with regard to race, hence this variable was not included in the analysis.

The comparison of cognitively impaired and cognitively intact participants in the evaluation age, education, socioeconomic status, baseline MMSE, baseline IADL, and the duration of the follow-up using t-tests did not result in any significant differences (Table 9). Comparison of the CI and IN groups with respect to their living arrangements (living alone versus not alone) using the Chi-square test did not detect any significant difference in this variable either (Table 9). The difference in the proportion of females in the CI group compared to IN group, using the binomial test, was not statistically significant (Table 9). The only statistically significant difference between the cognitively

impaired and intact groups was the proportion of people who have at least one APOE 4 allele (Table 9).

In addition, baseline performances on selected neuropsychological tests were compared for the cognitively impaired and intact. Because each of the Boston Naming, Visual Reproduction I and Visual Reproduction II tests had 108 cases missing, the results were considered unreliable and are omitted. As presented in the Table 10, the t-test comparison of the Boston Naming Test Abbreviated Version, Logical Memory I, Logical Memory II, Word List Acquisition, and Verbal Fluency (Animals) tests in the two groups did not reveal any statistically significant differences. The two groups were different in their performance on Delayed Recall and Verbal Fluency (Animals Fruits Vegetables) tests.

The number of blocks walked was split into quartiles and participants in different quartiles were compared with respect to their evaluation age, sex, education, socioeconomic status, years of follow-up, living arrangements (alone versus not alone), baseline MMSE score, baseline IADL and performance on neuropsychological tests (Tables 11 and 12). Even though underpowered for significant evaluation, the numbers for race are also included in the table because they seem to suggest the trend that majority of the participants in the 'black' and 'other' race group belong to the least active quartile. The only significantly different variables among the quartiles were sex, socioeconomic status and scores on the Boston Abbreviated Test. It is interesting to note that the number of female walkers decreases as the number of blocks walked increases. As a matter of fact, 76.36% of all inactive older adults (0 blocks per week) were females. This observation agrees with Centers for Disease Control and Prevention data that show older

females to be the least active segment of the population, and women to be less likely to participate in leisure-time activity than men.[41] Also, it is interesting to note in Table 11 that the older adults who do not walk have by far the lowest socioeconomic status.

A few participants reported a very high number of blocks walked per week (up to 50), so the same comparison was done restricting the highest quartile to less than 36 blocks. This restricted the data to just above the 95th percentile, and excluded five highest observations with values of 36, 48, and 50. The results of this comparison did not differ from what was found using unrestricted data (Table 13).

The number of hours exercised was split into quartiles, and participants in different quartiles were compared with respect to their baseline evaluation age, sex, education, socioeconomic status, years of follow-up, living arrangements (alone versus not alone), MMSE score, IADL score, and performance on neuropsychological tests (Tables 14 and 15). Despite the numbers too small for statistical comparison, the information on the race is reported in the table due to the same reasons explained in the section on walking. The only significantly different variables among the quartiles of hours exercised per week were living arrangement and age at onset. Although not statistically significant, the socioeconomic status and sex show the same pattern observed for the blocks walked per week. Women comprise 67.69% of those in the lowest quartile of hours exercised per week (<2 hrs), and the lowest SES is found in the lowest quartile as well.

Some of the participants reported unusually high number of hours exercised per week (range 0-120) as well. The five highest observations were 39, 42, 44, 63 and 120 hours of exercise. The data was subsequently restricted to <39 hours of exercise per week. The same comparison used on the unrestricted data was repeated here and results shown in the

Table 16. The living arrangement stayed marginally significant. Age at onset was no longer significant. The same patterns for the sex and SES were observed in this analysis as well.

Finally, the frequency of cognitive decline was compared among different quartiles for both blocks walked and hours exercised. The difference was statistically significant for the hours exercised, but not for the blocks walked per week (Table 17). The information reported in Table 17 is for the restricted data. The analysis on the unrestricted values was not different (Chi-square p value for the blocks walked = 0.3654; Chi-square p value for the hours exercised = 0.0099).

As presented in the Table 18, the categorical variable 'Activity', created by splitting Passive and Active Score along the median to create Low Active/Low Passive, Low Active/High Passive, High Active/High Passive, and High Active/Low Passive leisure activity participation groups, has a balanced distribution of participants among the 4 subcategories. Each group consists of approximately 50 people. When compared on a variety of baseline characteristics and neuropsychological tests performance, the participants in the four groups differed significantly only in their socioeconomic status (Tables 18 and 19). As discussed earlier, the findings from the analysis of blocks walked and hours exercised showed that the least active seniors had the lowest socioeconomic status. It is interesting to note that, in the case of Activity groups, the lowest SES is not found in the least active (Low Active/Low Passive), but in the Low Passive/High Active group.

The continuous variable 'Total Activity' (total number of points accrued for participation in all leisure activities regardless of their cognitive demand) was split into

quartiles and differences in baseline characteristics among quartiles was examined as well. This assessment was done to get additional insight into the leisure activities information that might otherwise be difficult to see. Overall, the differences among the participants in different quartiles were not significant, except for the mean age at onset (Table 20). When the same analysis was done by excluding the highest five observations, thus restricting the 4th quartile from 69.5 points to 58.5, the results did not change. In addition, the frequency of cognitive decline was compared among the quartiles using the Chi-square test. P values for both non-restricted and restricted data were not significant (p non-restricted 0.2624, p restricted 0.2668).

The participation in physical and leisure activities was not objectively measured, or verified with friends or family. Examining the correlation between certain variables was done to verify, to some extent, the information reported in the questionnaires. When examined as categorical variables (quartile split), the Pearson's correlation coefficient between the 'number of blocks walked' and the 'hours of light exercise per week' was 0.26. When examined as continuous variables, the coefficient was 0.18. This relationship was further examined by looking at the frequency table of quartiles of 'blocks walked' against quartile of 'hours of light exercise'. Looking diagonally across the table, the number of participants decreases as the numbers of hours spent in light exercise and numbers of blocks walked increase. The correlation between the 'Blocks Walked per Week' and 'Steps per Second' (gait) was checked for as well. The coefficient for this correlation was 0.094. For the correlation between the 'Hours of Light Exercise per Week' and 'Steps per Second' the coefficient was 0.10.

Preliminary Analysis Results

The results of the Kaplan-Meier analysis are available in Table 5. The results from the Verbal Fluency – Animals, Fruits, Vegetables test, as well as the Visual Reproduction 1, Visual Reproduction 2, and Boston Naming test were excluded from further analysis due to a very high number of missing observations. The survival curves for the MMSE were significantly different ($p = 0.0485$), as were the curves for the evaluation age ($p = 0.0027$), APOE status ($p = 0.0534$), Word acquisition test ($p = 0.0534$), Delayed Recall test ($p < 0.0001$), Verbal Fluency – Animals test ($p = 0.1019$), Exercise ($p = 0.0009$), Low active/ Low passive Leisure Activity group compared to all the others together ($p = 0.1024$), and Cohort ($p = 0.1462$). Both cohort indicator variables were also significant at 0.15 level (OBAS $p = 0.0594$, DPS $p = 0.1182$).

In addition, restricted hours of exercise and restricted blocks walked were tested. Both remained significant.

Further investigation of the differences among the four exercise quartiles suggested no difference between quartile 1 and quartile 2, or between quartile 3 and quartile 4. Consequently, the two lower quartiles were combined into one group, and the upper two into another. Hence, the 'Exercise' variable was recoded into 'Exercise Group' (EXgroup) variable, where 'EXgroup' = 1 for quartiles 3 and 4, and 'EXgroup' = 0 for quartiles 1 and 2. The Log-Rank test p value for this variable was <0.0001.

The univariate Cox analysis did not show any discrepancies with Kaplan-Meier analysis (Table 23).

Cox Proportional Hazards Models

1) Cox Proportional Hazards Model I – all participants, no MCIRS Variable

After all variables identified as significant in the preliminary analysis (Table 24) were entered into the model together only Evaluation age, APOE allele status, Delayed Recall and Exercise group remained significant. Consequently, they were retained in the model (Table 25a).

Interactions were evaluated, but none were significant at 0.05 level. In addition, both education and socioeconomic status were controlled for in the model, but remained non-significant (Table 25b).

In the first Cox model (Table 25b), higher scores on the Delayed Recall test were associated with a reduced risk of cognitive decline. Participants with a one point increase in this test experience cognitive decline at a rate that is 25% lower than the participants at the lower score (95% CI 13%, 36%). Exercising more than 4 hours per week was also associated with a reduced risk of cognitive decline. According to this model, participants who exercise more than 4 hours per week experience cognitive decline at a rate that is 69% lower than participants who exercise 4 hours or less a week (95% CI 40%, 84%). The estimated hazard ratio suggests important benefit of exercise, controlling for all other variables in the model.

In this model, the proportional hazards assumption was met for the evaluation age, delayed recall and exercise group, but it was violated for the APOE status, sex and

education. Some of the violation of the assumption can probably be attributed to the effect imparted by the younger participants who take longer to develop cognitive impairment, and in return affect the appearance of the hazard function. This is accounted for by the age-adjusted model. The overall robustness of the Cox model and satisfaction of the proportional hazards assumption for the significant variables is believed to support the adequacy of the model for this analysis.

2) Cox Proportional Hazards Model II – Complete Case Analysis

The second Cox model was developed using the complete data set and the selection of variables identified as significant in the preliminary analysis (Table 24). This model is not significantly different from the Cox I model. Parameter estimates have not changed significantly, and the same variables have been selected into the model. Compared with the Cox I, the evaluation age is no longer significant, while everything else remained the same (Table 26a).

The interaction between OBAS cohort and evaluation age was the only significant term, and consequently it was entered into the model (Table 26b). This significant interaction reflects the exclusion of 76 OBAS subjects from the complete case analysis. Finally, confounders sex and education were included into the model, but they remained non significant (Table 26c).

In the Cox model II (Table 26c), higher scores on the Delayed Recall test remained associated with a reduced risk of cognitive decline. Participants with one point increase in

this test are experiencing cognitive decline at a rate that is 30% lower than the participants at the lower score (95% CI 8%, 44%).

The association of the Exercise variable with a reduced risk of cognitive decline lost statistical significance, most likely due to small sample size.

The model suggests that the subset of subjects used in the complete case analysis was consistent with the total sample.

In addition, development of the separate model for MCRIS subset was attempted using BACKWARD selection. It arrived at entirely different subset of variables that did not intuitively make sense. This model demonstrated the danger of relying on automated procedures that do not have the ability to incorporate common sense and grasp the meaning of the data outside of statistical computations. The lesson from this attempt was that automated procedures should be used with caution and only as an aid, not as a guiding method in model building.

3) Cox Proportional Hazards Model III

3.1) Linear Regression Model for The Multiple Imputation – Selecting the Best Model for Predicting the Missing MCIRS Values from the Other Variables in the Data Set

Upon exclusion of the variables that had no relevance for the model, variables that had large numbers of missing values, and variables that were selected for elimination based on correlation criteria, the total number of variables available for the further

analysis was 19 (Table 27). Simple linear regression (SLR) conducted on these 19 variables identified the selection of significant variables for the inclusion into the model building (Table 28). Starting with the variables selected by SLR and using automated Adjusted R Squared (ADJRSQ) procedure, the multiple linear regression (MLR) model with the highest Adjusted R^2 value ($R^2 = 0.3139$) was selected (Table 29a). The model was examined for gross departures from normality. The normal probability plot did not depart substantially from the 45° line, suggesting linearity (Figure 1a). The plot of studentized residuals against predicted values did not demonstrate any particular pattern, suggesting no major violations either (Figure 1b). Consequently, this model (Table 29a) was considered adequate for the purpose of prediction.

3.2) Cox Proportional Hazards Model III – Model Including Imputed MCIRS Variable

After the imputed MCIRS variable, along with the other variables identified as significant in the preliminary analysis, (Table 24) were included together into the model, only Evaluation age, APOE status, Delayed Recall and Exercise group remained significant (Table 29b). To arrive at the final Cox III model, the important confounders, sex and education, were added to the model. Interactions were evaluated, but none were significant.

The final model (Table 29c) further confirmed the adequacy of the first Cox model. The same variables were retained in the model. The MCIRS variable was included in the model as an important confounder, but remained insignificant. Higher

scores on Delayed Recall test were still associated with the reduced risk of cognitive decline. Participants with one point increase in this test experience cognitive decline at a rate that is 24% lower than the participants at the lower score (95% CI 10%, 37%). Exercising more than 4 hours per week also remained associated with the reduced risk of cognitive decline. Participants who exercise more than 4 hours per week experience cognitive decline at a rate that is 71% lower than participants who exercise 4 hours or less (95% CI 34%, 87%). The estimated hazard ratio in this model as well suggests the important benefit of exercise, controlling for all other variables in the model.

In summary, three different Cox proportional hazards models were developed (Table 30). Overall, all of the models were similar, with some differences in the complete case analysis due to reduced sample size. The models demonstrated a significant association between Exercise and Delayed Recall test and cognitive decline.

DISCUSSION

Design and Results Summary

This study quantified the independent effects of walking, exercise and participation in leisure activities on cognitive function in older adults. The relationship between physical activities and leisure activities at the study baseline and the time until progression to cognitive decline was analyzed.

The prospective cohort of 212 older adults, 75 to 97 years of age, was followed for an average of 4.1 years. At the study baseline, all of the 128 female and 84 male participants

were independently functioning, depression free, and cognitively intact community dwellers in relatively good health. The information on their participation in leisure activities, exercise (number of hours per week) and walking (number of blocks per week) at the study baseline was reported in the Personal and Family History Form, as well as their performance on the battery of neuropsychological tests. On average, this cohort exercised 7 hours and walked 9 blocks per week. According to their cognitive demand, leisure activities were categorized into cognitively passive and cognitively active. The frequency of participation in each activity was reported, and points assigned for each level of participation according to the Modified Verghese[18] scale. This scale assigns one point to participation in one activity for one day per week. The average score for participation in cognitively active leisure activities was 21.61, and average score for the passive activities was 12.35. The mean score for the Total Activity was 33.96. To allow for the comparison of the time until progression to cognitive decline among different levels of participation in active and passive leisure activities, the participants were further categorized into 4 subgroups by splitting the Active and Passive scores along the median. The resulting Low Active/Low Passive, Low Active/High Passive, High Active/High Passive, and High Active/Low Passive leisure activity participation groups were reasonably well balanced, having around 50 participants each.

Cognitive decline was defined as repeated abnormal scores on MMSE (<24) or CDR (>=0.5) on two consecutive assessments. Age of onset was defined as the age at the time the participant received the first of the two consecutive abnormal scores on MMSE or CDR.

Fifty two participants, 31 females and 21 males, had developed cognitive decline by the end of the study period, with a mean age of onset of 89.98 years.

This study controlled for important confounders, such as sex and education. The health status variable MCIRS was missing for 37% of the participants. This shortcoming was addressed using multiple imputation. The missing MCIRS values were predicted using variables from the data set as covariates. Consequently, the MCIRS scores were available for the entire study population, and this variable could be controlled in the study as well.

The cognitively impaired and cognitively intact groups were compared on a variety of demographic and baseline characteristics, as well as performance on the neuropsychological tests. The proportion of people who have at least one APOE 4 allele and performance on Delayed Recall and Verbal Fluency (Animals Fruits Vegetables) tests were the only statistically significant differences between the two.

Comparison of the participants in different quartiles of blocks walked per week showed that they differ significantly only in sex and SES, with 76.36% of all inactive older adults (0 blocks walked) being female.

The participants in different quartiles of hours exercised per week differed only in their age at onset of cognitive decline and living arrangements (alone versus not alone). Although not statistically significant, socioeconomic status and sex exhibit the same pattern observed for the blocks walked per week. The majority of the least active exercisers are women. SES status is also the lowest for this group.

The frequency of cognitive decline among different quartiles of hours exercised was significantly different, but not for quartiles of blocks walked per week.

Three different multivariate Cox proportional hazards models were developed to test the study hypotheses. The first model was developed using all study participants, regardless of the availability of their MCIRS scores. The MCIRS variable itself was not included in this model because of large number of missing values. Next, a complete case analysis was conducted to validate the first model. Finally, the missing data were imputed and the final model was developed using the imputed MCIRS values.

In the first model, exercising more than 4 hours per week was associated with a reduced risk of cognitive decline. Participants who exercise more than 4 hours per week experience cognitive decline at a rate that is 69.2% lower than participants who exercise 4 hours or less (95% CI 40%, 84.2%). In addition, higher scores on Delayed Recall test were associated with a reduced risk of cognitive decline. Participants with one point increase in this test experience cognitive decline at a rate that is 25% lower than the participants at the lower score (95% CI 12.8%, 35.5%).

In the complete case analysis, higher scores on Delayed Recall test remained associated with the reduced risk of cognitive decline. Participants with one point increase in this test are experiencing cognitive decline at a rate that is 29.7% lower than the participants at the lower score (95% CI 43.6%, 7.8%). After controlling for sex and education, the association of exercise with a reduced risk of cognitive decline lost significance, most likely due to reduced sample size. Regardless, this model closely resembles the first one. This suggests that the participants for whom MCIRS information was not available might be a random sub-sample of the entire study population.

The final Cox model retained the same selection of variables as previous models, including the MCIRS variable that was added as an additional important confounder. The

choice and the extent of participation in leisure activities could be considerably affected by health conditions. For this reason, inclusion of the MCIRS variable into the analysis was considered to be of critical importance. Exercising more than 4 hours per week remained associated with a reduced risk of cognitive decline. Participants who exercise more than 4 hours per week experience cognitive decline at a rate that is 70.6% lower than participants who exercise 4 hours or less. (95% CI 34%, 86.9%). Higher scores on Delayed Recall test were still associated with a reduced risk of cognitive decline. Participants with one point increase in this test experience cognitive decline at a rate that is 24.4% lower than the participants at a lower score (95% CI 9.9%, 36.5%). The MCIRS variable remained non-significant.

In the preliminary analysis leisure activities, measured either as categorical or continuous variable, demonstrated statistical significance. The Kaplan-Meier analysis detected a significant difference in the survival curve of the least active leisure activity group (Low active/ Low passive) when compared to all other groups together (0.1024). The univariate Cox regression of the continuous 'Total Activity' variable yielded significant results as well (0.0274). Upon inclusion into multivariate Cox models neither remained significant.

This study demonstrates a significant association between participation in 4 or more hours of exercise per week and reduced risk of cognitive impairment (HR 0.294; 95% CI 0.131, 0.660). The association remains even after adjustment for sex, education and health status. One point increase in Delayed Recall test was also associated with a reduced risk of cognitive impairment (HR 0.765; 95% CI 0.635, 0.901). However, the study did not demonstrate an association between participation in leisure activities and

risk of cognitive impairment. The null results could represent a true lack of association, but the small sample size or unmeasured confounding could also be the possible explanations.

Study Limitations

The analysis in this study was based on 212 older adults. This was a relatively small sample size. The research on cognitive functioning in older adults has been a relatively new addition to the field of epidemiology. The cohorts used in this study (OBAS, DPS, AADAPt) are fairly new as well, and were specifically created to research the cognitive functioning in the elderly. Although other prospective cohorts designed to explore the aging related issues do exist nation-wide, these three cohorts provide a unique opportunity to investigate the aging processes in Oregonians. Given these circumstances and relative newness of the cohorts, despite its sample size this study can be viewed as a pilot that can give a good sense of direction for future research.

The frequency of participation in leisure activities reported in the questionnaires was not objectively measured nor verified with participants' families or friends. The data consists solely of self-reported values, and therefore is prone to misclassification. An attempt was made to statistically validate at least some of the reported information. Where applicable (e.g. variables 'hours exercised' and 'blocks walked') the analysis was repeated excluding the unusually high observations, and findings for the restricted data were reported as well. In addition, we expected some of the variables to be highly correlated and checked their Pearson's correlation coefficients. The rationale that self-reported light

exercise and walking would be positively associated stems from the idea that leading a physically active or passive life style should be equally reflected in both variables. When the two variables were tested as categorical (quartile split) the Pearson's correlation coefficient was 0.26, and even lower (0.18) when they were tested as continuous variables. Also, the idea that the faster gait reflects better overall physical condition was examined. The correlation between 'blocks walked per week' and 'steps per second' was positive but low (Pearson's correlation coefficient 0.094). Similar results were observed for the correlation between light exercise and gait (Pearson's correlation coefficient 0.10). This study clearly demonstrates the importance of direct measurement, or at least verification of the participation in the activities under the investigation, and the need for this issue to be adequately addressed in the further research, turning this limitation into one of this study's most important findings.

The 212 study subjects included only 21 non-white participants (7% African-Americans, 1% Hispanics, 1% Asian-Americans and 1% Native-Americans), of whom only one developed cognitive impairment. With the numbers so low, any valid inferences regarding race could not be made, and consequently this variable was not used in the analysis. The recruitment and maintenance of more non-white cohorts, such as AADAPt, should be a high priority in the area of research on cognitive functioning in elderly. On the other hand, the racial composition of the study population in this analysis closely resembles the racial composition of the Portland Metropolitan Area. According to the Census data for the year 2000,[42] 78% of the population in the Portland Metropolitan Area was white, 7% black and only 1% Native American.

According to the Census data for the year 2000, 45% of the population 65 years of age or older in the Portland Metropolitan Area live with disabilities.[42] On the other hand, the overall health of the cohorts used in this study, especially OBAS, is above the average. This study sample is highly selected, and therefore not representative of all older adults in Portland Metropolitan Area. This does not affect the internal validity of the study, but caution should be exercised with respect to generalizability to non-white older adults of average (or less) health.

Finally, the graphical examination of proportional hazards assumption revealed that it was not met for all variables in the Cox regression models. In some instances the graphs of hazard functions against the follow-up time show sudden decline. One possible explanation for this drop in hazard is the influence of the youngest participants in the sample. They stay in the study longer and also take longer to get to the age where they begin experiencing the cognitive decline, thus making it look as if the hazard drops suddenly. Regardless, the overall robustness[43] of the Cox model and satisfied proportional hazards assumption for the significant variables in the model sufficiently support model adequacy.

Study Advantages

A number of advantages set this study apart from its predecessors.

First, the data for the study were collected on a prospective cohort of older adults. The major benefit of the prospective design is the ability to establish participation in leisure and physical activities prior to incidence of cognitive decline. Thus, the exposure precedes outcome providing for the clearer test of direction of the association under

investigation. Some of the previous research was unable to eliminate the possibility that cognitively impaired adults as a consequence choose to participate in the leisure activities that are less cognitively demanding, while cognitively intact seniors choose the more demanding activities. By the nature of its prospective design this study has been able to avoid the inclusion of cognitively impaired participants into the cohort, and consequently addresses this concern.

The second strength of this analysis was in the way it addressed the problem of the missing data. It is well recognized that missing data can potentially create a biased sample and hence distort relationships observed among variables under investigation. To address this problem, several different ways of dealing with the missing data have been developed. One is to delete the missing cases to produce a complete data set. This method can result in a biased subset that is not representative of the entire sample from which it was created. Another common method is mean substitution, where the missing data are replaced with the mean value of the complete data set for the variable in question. Since the same value replaces each missing case, this method artificially reduces the variance of the variable in question.[44] Another option is to predict missing values using regression. In this method missing values are imputed using the model based on the other variables in the data set. This method is somewhat better than the first two because it uses relationships present among the variables, but its disadvantage lies in the fact that it underestimates the variance of the parameter estimates.[45] To appropriately address the shortcomings of the previously described approaches, the method of multiple imputation was used in this study. It is one of the most sophisticated methods currently available to address the problem of missing data. The requirement for this approach is that the data

are missing at random. When this is the case, the missing data depend on the known values and can be described using the variables available in the data set. If this requirement is satisfied, the missing values are predicted using existing values from the other variables in the data set. Once predicted, these values are substituted for the missing values resulting in a complete data set called 'imputed data set'. The process of imputation is repeated, most commonly 3 to 10 times, to produce multiple imputed data sets. Analysis is then carried out on each of those sets yielding multiple results. Finally, these results are combined to generate one overall analysis. The advantage of the multiple imputation over the other methods previously described is that it adequately preserves the variability in the missing data and accounts for the uncertainty caused by estimation. Also, it produces unbiased parameter estimates, it is robust to departures from normality assumptions, and it works well for the high numbers of missing values and the small sample size.[44]

The parent study collected extensive information on demographics, social factors, health factors, and psychoneurologic function, allowing this study to control for the most important confounders. In addition, the exclusion criteria for this study were carefully designed, keeping a variety of other potential influences in mind. Consequently, at the study baseline the cohort was older than 75 years of age, functionally independent and depression free. In addition, the outcome was measured using validated clinical assessment.

This study goes one step beyond the question of whether participation in leisure activities is associated with a lower risk of cognitive decline. The design of the current study recognizes that it might not be activity in general, but a specific type of activity that

influences the relationship under question. Hence, the exposure in this study is defined in a way that recognizes the cognitive demand of the variety of activities in which seniors generally engage. In addition, the study addresses the potential association of physical activity with cognitive function separately, further separating a tangle of leisure categories encountered in the previous research. This separation enables the study to pin point the specific risk factors that might be at play. This approach to the leisure activities was undertaken with the development of prevention strategies in mind. It would be very difficult, if not impossible, to design effective prevention strategies unless the research offers specific recommendations for the maintenance of cognitive abilities in older adults.

Future Research

To further enhance our understanding of the relationship between participation in the leisure activities and reduced risk of cognitive decline, the future research should aim to incorporate valuable lessons learned from this study.

First of all, to provide for the stronger analysis of the relationship in question any future research should look for the adequate ways to increase the sample size. In addition, the racial diversity of the study population should be increased as well. This would allow for the inferences to be made about non-white older adults as well, and consequently increase generalizability of the findings.

In addition, the identification of the specific risk factors for cognitive impairment is of crucial importance for the development of successful and meaningful interventions and recommendations for the preservation of cognitive functioning in elderly. This can only be achieved through the appropriate categorization of the exposure of interest. The effective categorization, in turn, is affected by the availability and quality of the exposure information collected. In the future studies, an attempt should be made to collect the information on leisure activities in a more precise manner. The questionnaires should be designed to request the information on the leisure activities in a way that leaves no room for self-interpretation or misunderstanding. Questions on the frequency of participation should be designed in a way that minimizes bias due to self-reporting. In fact, direct measurement and verification of the self-reported information should be attempted very seriously. Considering that validity of inferences we draw from any study depend on the quality of the data at hand, it is obvious that investing the time and funding to address the concerns surrounding self-reporting is of critical importance.

Implications for the Public Health

This study is adds support to the body of work that demonstrated the beneficial effects of physical exercise on healthy aging. Because of its importance, more work is needed to develop successful strategies that will help to promote and incorporate physical exercise as a part of the daily routine among older adults. To facilitate the process of behavior change in this population, an effort should be made to develop feasible and easy to understand recommendations regarding both the type and the frequency of

participation. In addition, the programs should focus on developing effective strategies to overcome barriers that might prevent an otherwise informed older person from exercising.

Finally, this study identifies older females as the least active older adults, recognizing the need for research and prevention strategies that would specifically target this population.

TABLES

Table 3. Leisure Activities Reported in the Baseline Questionnaire and Associated Average Participation Scores[1,2]

Cognitively Active Leisure Activities	**Mean**	**Std. Dev.**
Owning and caring for pet	1.5	2.88
Have visitors	1.65	2.56
Visit others at their homes	1.06	1.66
Going out to eat	0.9	1.11
Attending a club or group meeting	0.61	0.88
Attending church/synagogue services	0.91	1.51
Listening to a TV or radio news program	6.38	1.93
Listening to music	4.16	3.17
Watching a favorite TV or sports program	4.37	3.1
Watching a movie	0.85	1.67
Cognitively Passive Leisure Activities		
Traveling out of town	0.2	0.3
Spending time at a hobby or game	2.16	2.82
Reading a newspaper	5.82	2.5
Reading an entire book	1.02	1.9
Following finances or investments	2.43	3.06
Taking a class	0.29	0.92
Using a computer	1.3	2.67

[1] One point assigned for participation in one activity for one day per week.
[2] Score range on all activities 0-7, except for Traveling out of town 0-1

Table 5. Variable Explanation, Categorization and Univariate Kaplan-Meier Analysis Summary

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
Cohort membership	OBAS, DPS, AADAPt	Categorical	Original form			**0.1462**
			OBAS Cohort Indicator Variable	OBAS (1) vs. other cohorts (0)		**0.0594**
			DPS Cohort Indicator Variable	DPS (1) vs. other cohorts (0)		**0.1182**
Socioeconomic Status	Hollingshead Socioeconomic Status Score	Continuous	Median Split	Median = 47		0.9151
			Quartile Split	Q1 36, Q2 47, Q3 55, Q4 66		0.9472
Education	Education in years	Continuous	Median Split	Median = 14		0.2286
			High School Split	12 years of education		0.8
Sex	Male, female	Categorical				0.6494
Ethnicity	White, Black, other	Categorical				
Marital Status	Married, remarried, divorced, widowed,	Categorical				

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
	not married					
Place of Residence	Apartment or home, retirement community	Categorical				
Living Arrangements	Alone, not alone	Categorical				0.26
Age at Entry	Age at entry into the Cohort	Continuous				
Evaluation Age	Age at entry into this study	Continuous	Median Split	Median = 86.1		**0.0027**
Age at Last Evaluation		Continuous				
Onset Age (new)	Age at the onset of cognitive impairment.	Continuous				
MMSE	Mini Mental State Examination	Continuous	Median Split	Median = 28		**0.0458**
IADL	Independent Activities of Daily Living	Continuous	Split at the value of interest	0 vs. > 0		0.3802

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
APOE allele 4 Status	At least one APOE 4 allele versus none	Categorical		Yes vs. No		**0.0534**
Steps per Second	Gait	Continuous				
MCIRS	Modified Illness Rating Scale Scores	Continuous	Median Split	Median = 21		**0.1199**
Follow-up	The time in years a participant was followed for in this study	Continuous				
Status	Cognitively Impaired vs. Cognitively Intact	Categorical				
Word Acquisition	Neuropsychological Test	Continuous	Median Split	Median = 18		**0.1066**
Delayed Recall	Neuropsychological Test	Continuous	Median Split	Median = 6		**<0.0001**
Verbal Fluency Test – Animals	Neuropsychological Test	Continuous	Median Split	Median = 17		**0.1019**

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
Verbal Fluency Test- Animals, Fruits, Vegetables	Neuropsychological Test	Continuous				
Logical Memory I	Neuropsychological Test	Continuous	Median Split	Median = 12		0.3499
Logical Memory II	Neuropsychological Test	Continuous	Median Split	Median = 9		0.163
Visual Reproduction 1	Neuropsychological Test	Continuous				
Visual Reproduction 2	Neuropsychological Test	Continuous				
Boston Naming Abbreviated Test	Neuropsychological Test	Continuous	Median Split	Median = 14		0.3162
Boston Naming Test	Neuropsychological Test	Continuous				
Blocks Walked	Blocks Walked per Week	Continuous	Quartiles of Blocks Walked	Quartile Split: Q1 0, Q2 6, Q3 12, Q4 50		0.9148

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
			Restricted Quartiles of Blocks Walked	Quartile split, Q4 restricted to <36		0.9185
			Blocks Median (Median Split of the Continuous 'Blocks Walked')	Median = 6		0.5027
Exercise	Number of hours exercised per week	Continuous	Quartile of Hours Exercised	Quartile split: Q1 2, Q2 4, Q3 8, Q4 120		**0.0009**
				Q1 vs. Q2		0.4679
				Q1 vs. Q3		**0.0026**
				Q1 vs. Q4		**0.0417**
				Q2 vs. Q3		**0.0002**
				Q2 vs. Q4		**0.0092**
				Q3 vs. Q4		0.5547
			Restricted Quartiles of Hours Exercised	Quartile split, Q4 restricted to <39		**0.0008**
			Exercise Group	Exercise quarters split into two groups.		**<0.0001**

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
				Exercise Group = 1 for the 3rd and 4th Q, else = 0.		
Passive Score	Total number of points accrued for participation in cognitively passive leisure activities	Continuous	See "Activity Group" below			
Active Score	Total number of points accrued for participation in cognitively active leisure activities	Continuous	See "Activity Group" below			
			Activity Group: median split of Active and Passive score to create low active/ low passive, low active/ high passive, high active/ low passive, high active/ high passive groups	Median active score = 20.50 Median passive score = 11		0.3616

Variable	Variable Explanation	Original Variable Type	New Categorization of the Variable	Explanation of the New Categorization	Parameter Estimate	P value[1,2]
			Activity0 Group: How Low/Low group compares to all others together			**0.1024**
Total Activity	Total number of points accrued for participation in all leisure activities regardless of their cognitive demand	Continuous	Q1 27, Q2 34, Q3 40.5, Q4 69.5			**0.1487**

1 Log-rank Test

2 p-values < 0.15 are highlighted and considered statistically significant

Table 6. Study population

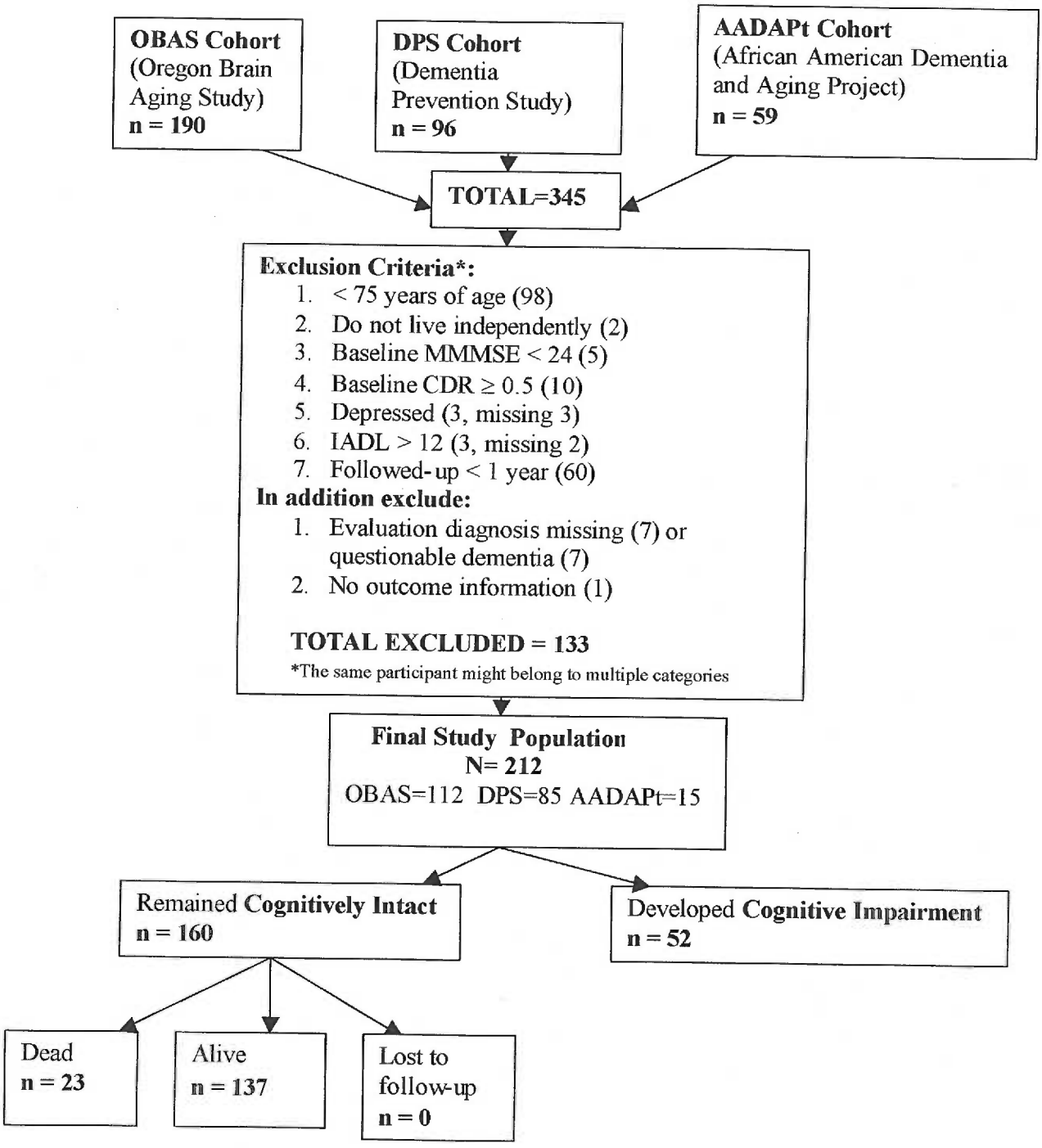

Table 7. Descriptive Statistics for Continuous and Categorical Variables

Continuous Variable Summary			
Variable	**N**	**Mean**	**Std. Dev.**
Evaluation Age	212	85.27	4.77
Education	211	13.96	2.54
Socioeconomic Status	210	45.55	11.68
Follow-up	212	4.08	2.88
Onset Age (new)	52	89.98	4.58
MMSE	212	28.22	1.45
IADL	212	0.09	0.35
Steps per Second	210	1.77	0.24
Passive Score	212	12.35	6.15
Active Score	212	21.61	8.25
Blocks	212	8.99	10.37
Exercise	205	7.20	11.51
Total Activity	212	33.96	10.31
MCIRS	134	20.62	3.84
Word Acquisition	209	18.51	3.64
Delayed Recall	209	6.02	1.99
Visual Reproduction 1	104	28.50	6.05
Visual Reproduction 2	104	20.20	9.10
Animals	208	16.89	4.44
Animals Fruits Vegetables	128	41.44	9.08
Boston N Abbreviated Test	194	14.11	0.99
Boston Naming Test	104	53.24	5.21
Logical Memory I	211	11.71	4.28
Logical Memory II	211	9.29	4.78

Categorical Variable Summary	
Variable	**%**
Place of Residence	
Home/Apartment	76.4
Retirement Community	23.6
Marital Status	
Married/Remarried	39.6
Not married/Divorced/Widowed	60.4
Sex	
Male	39.6
Female	60.4
Living Arrangement	
Alone	57.1
Not alone	42.9
APOE allele 4 Status	
Yes	18.1
No	81.9

Table 8. Cohort Comparison Summary

	AADAPt	DPS	OBAS	P value
Age	79.2 (3.85)[1]	87.27 (2.22)	84.57 (5.39)	<0.0001[2]
Education	12.8 (2.93)	13.49 (2.47)	14.47 (2.45)	0.0047[2]
SES	34.79 (11.51)	44.62 (10.58)	47.6 (11.75)	0.0003[2]
Follow-up (years)	1.47 (0.4)	2.48 (0.54)	5.68 (3.17)	<0.0001[2]
MMSE	27.73 (1.87)	28.29 (1.36)	28.23 (1.45)	0.384[2]
Sex (%)				0.3324[3]
Males	26.7	36.5	43.75	
Females	73.3	63.5	56.25	
Race (%)				
White	0	96.5	97.3	
Black	100	0	0	
Asian Amer.	0	2.3	0	
Native Amer.	0	1.2	0.9	
Hispanic	0	0	1.8	

[1] Mean (SD)
[2] One-way ANOVA
[3] Chi-square Test

Table 9. Baseline Characteristics of Participants in Whom Cognitive Impairment (CI) Developed and in Whom it Did Not (IN)

	Cognitively Impaired (n=52)	**Cognitively Intact (n=160)**	**P value**
Mean evaluation age (yr)	86.02 (SD ±4.62)	85.03 (SD±4.80)	0.1823[1]
Mean education (yr)	14.27 (SD ±2.59)	13.86 (SD ±2.53)	0.2928[1]
Mean SES	47.44 (SD ±12.09)	44.93 (SD ±11.51)	0.1698[1]
Mean duration of follow-up (yr)	3.96 (SD ±2.52)	4.14 (SD ±2.99)	0.9574[1]
Mean age at onset (yr)	89.98 (SD ±4.58)	N/A	
Mean baseline MMSE score	27.90 (SD ±1.56)	28.33 (SD ±1.40)	0.0910[1]
Mean baseline IADL	0.135 (SD ±0.49)	0.08 (SD ±0.30)	0.6129[1]
SEX Female	31	97	0.9857[2,4]
Living arrangements			0.9176[3]
Alone	30	91	
Not alone	22	69	
At least one APOE ∈ 4 present	16	21	**0.0012[2,5]**

[1] Wilcoxon test
[2] Binomial test
[3] Chi-square test
[4] Testing for the difference in the proportion of females in CI compared to IN group
[5] Testing for the difference in proportion of people with at least one APOE allele 4 between IN and CI

Table 10. Baseline Performance on Neuropsychological Battery Tests for Cognitively Impaired and Cognitively Intact Groups and t-Test Comparison of the Scores

	Cognitively Impaired[1] (n = 56)	**Cognitively Intact[1] (n = 168)**	**P value[2]**
Boston Naming Test Abbreviated Version	14.20 (0.83)	14.08 (1.04)	0.4962
Logical Memory I	12.61 (4.06)	11.42 (4.32)	0.0842
Logical Memory II	10.00 (4.57)	9.06 (4.84)	0.2237
Word List Acquisition	17.66 (4.07)	18.78 (3.46)	0.0575
World List Delayed Recall	5.47 (2.19)	6.20 (1.90)	**0.0223**
Animals	16.26 (4.27)	17.09 (4.48)	0.2469
Animals Fruits Vegetables	37.68 (8.63)	42.35 (8.99)	**0.0205**

[1] Mean (SD)
[2] t-Test

Table 11. Baseline Characteristics of Participants by Quartiles of Blocks Walked Per Week

	1st Quartile (0 blocks) N = 55	2nd Quartile (0-6 blocks) N = 63	3rd Quartile (6-12 blocks) N = 52	4th Quartile (12-50 blocks) N = 42	P value
Mean evaluation age (yr)	84.99 (SD±5.29)	86.25 (SD±4.64)	84.59 (SD±4.53)	85.02 (SD±4.45)	0.2630*
Mean education (yr)	13.33 (SD±2.31)	14.39 (SD±2.63)	14.29 (SD±2.82)	13.76 (SD±2.22)	0.0984*
Mean SES	41.24 (SD±10.22)	47.84 (SD±12.19)	45.98 (SD±11.58)	47.19 (SD±11.71)	**0.0130***
Mean years of follow-up	3.97 (SD±2.97)	3.77 (SD±2.60)	4.81 (SD±3.10)	3.87 (SD±2.81)	0.2221*
Mean age at onset (yr)	90.28 (SD±4.83)	90.51 (SD±4.19)	90.07 (SD±4.44)	88.95 (SD±5.37)	0.8641*
Mean baseline MMSE score	28.09 (SD±1.57)	28.57 (SD±1.11)	28.17 (SD±1.68)	27.93 (SD±1.37)	0.1159*
Mean baseline IADL	0.15 (SD± 0.36)	0.11 (SD±0.48)	0.06 (SD±0.24)	0.05 (SD±0.22)	0.4584*
SEX					**0.0347****
Female	42	37	27	22	
Male	13	26	25	20	
Living					0.3578**
Alone	31	41	29	20	
Not Alone	24	22	23	22	
RACE					
White	45	60	49	37	
Black	7	2	3	3	
Other	3	1	0	2	

* One-way ANOVA
** Chi-square test

Table 12. Baseline Performance on Neuropsychological Tests by Quartiles of Blocks Walked

	Q1 (0 b) N = 55	Q2 (0-6 b) N = 63	Q3 (6-12 b) N = 52	Q4 (12-50 b) N = 42	P value[2]
Word Acquisition	18.62 (3.94)	18.71 (3.61)	18.68 (3.45)	17.86 (3.52)	0.6045
Delayed Recall	6.36 (1.95)	6.15 (2.15)	5.92 (1.88)	5.52 (1.90)	0.2036
Animals	17.42 (5.08)	16.72 (4.95)	16.44 (3.62)	17.00 (3.63)	0.7064
Boston Abbreviated	13.81 (1.10)	14.28 (0.83)	14.39 (0.67)	13.92 (1.17)	**0.0084**
Logical Memory I	11.47 (4.78)	12.08 (4.02)	11.88 (3.69)	11.24 (4.45)	0.7484
Logical Memory II	9.75 (4.84)	9.87 (4.82)	8.94 (4.69)	8.24 (4.73)	0.2925

[1] b = Blocks Walked
[2] One-way ANOVA

Table 13. Baseline Characteristics of Participants by Quartiles of Restricted Blocks Walked Per Week

	1st Quartile (0 blocks) N = 55	2nd Quartile (0-6 blocks) N = 63	3rd Quartile (6-12 blocks) N = 52	4th Quartile (12-30 blocks) N = 32	P value
Mean evaluation age (yr)	84.99 (SD±5.29)	86.25 (SD±4.64)	84.59 (SD±4.53)	84.89 (SD±4.50)	0.2576*
Mean education (yr)	13.33 (SD±2.31)	14.39 (SD±2.63)	14.29 (SD±2.82)	13.69 (SD±2.18)	0.0958*
Mean SES	41.24 (SD±10.22)	47.84 (SD±12.19)	45.98 (SD±11.58)	47.19 (SD±11.59)	**0.0140***
Mean years of follow-up	3.97 (SD±2.97)	3.77 (SD±2.60)	4.81 (SD± 3.10)	4.04 (SD±2.91)	0.2547*
Mean age at onset (yr)	90.28 (SD±4.83)	90.51 (SD±4.19)	90.07 (SD±4.44)	88.84 (SD±4.57)	0.8496*
Mean baseline MMSE score	28.09 (SD±1.57)	28.57 (SD±1.12)	28.17 (SD±1.68)	27.84 (SD±1.37)	0.0966*
Mean baseline IADL	0.15 (SD±0.36)	0.11 (SD±0.48)	0.058 (SD±0.24)	0.063 (SD±0.25)	0.5749*
SEX					**0.0417****
Female	42	37	27	17	
Male	13	26	25	15	
Living					0.5122**
Alone	31	41	29	16	
Not Alone	24	22	23	16	
RACE					
White	45	60	49	27	
Black	7	2	3	3	
Other	3	1	0	2	

* One-way ANOVA

** Chi-square test

Table 14. Baseline Characteristics of Participants by Quartiles of Hours Exercised Per Week

	1st Quartile (≤ 2 hrs) N = 65	2nd Quartile (2-4 hrs) N = 39	3rd Quartile (4-8 hrs) N = 53	4th Quartile (8-120 hrs) N = 48	P value
Mean evaluation age (yr)	86.28 (SD±4.61)	85.77 (SD±4.96)	84.89 (SD±4.66)	84.03 (SD±4.77)	0.0752*
Mean education (yr)	13.57 (SD±2.27)	14.26 (SD±2.23)	14.19 (SD±2.78)	14.04 (SD±2.69)	0.4548*
Mean SES	43.57 (SD±12.19)	48.59 (SD±10.04)	45.69 (SD±12.48)	45.13 (SD±11.42)	0.2121*
Mean follow-up (yr)	3.73 (SD±2.71)	3.50 (SD±2.31)	4.77 (SD±3.11)	4.39 (SD±3.27)	0.1124*
Mean age at onset (yr)	91.60 (SD±3.86)	89.57 (SD±4.79)	90.63 (SD±4.53)	86.25 (SD±4.60)	**0.0390****
Mean baseline MMSE score	28.26 (SD±1.54)	27.90 (SD±1.52)	28.51 (SD±1.30)	28.04 (SD±1.38)	0.1859*
Mean baseline IADL	0.11 (SD±0.31)	0.21 (SD±0.61)	0.04 (SD±0.19)	0.04 (SD±0.2)	0.0925*
SEX					0.1834**
Female	44	25	31	23	
Male	21	14	22	25	
Living					**0.0329****
Alone	45	19	32	21	
Not Alone	20	20	21	27	
RACE					
White	56	37	50	42	
Black	6	2	2	4	
Other	3	0	1	2	

* One-way ANOVA
** Chi-square test

Table 15. Baseline Performance[1] on Neuropsychological Tests by Quartiles of Hours Exercised per Week

	Q1 (≤ 2 hrs) N = 65	Q2 (2-4 hrs) N = 39	Q3 (4-8 hrs) N = 53	Q4 (8-120 hrs) N = 48	P value[2]
Word Acquisition	18.66 (4.05)	18.03 (3.97)	19.25 (3.20)	17.91 (3.32)	0.2504
Delayed Recall	6.27 (1.97)	5.62 (2.51)	6.19 (1.74)	5.77 (1.92)	0.3085
Animals	16.93 (5.20)	16.79 (4.34)	17.54 (4.67)	16.43 (3.15)	0.6630
Boston Abbreviated	13.98 (0.97)	14.03 (1.13)	14.24 (0.90)	14.20 (1.01)	0.4907
Logical Memory I	11.94 (4.32)	10.87 (3.75)	11.83 (4.61)	11.98 (4.40)	0.5991
Logical Memory II	9.32 (4.42)	8.90 (4.35)	9.70 (5.36)	8.89 (5.11)	0.8172

[1] Mean (SD)
[2] One-way ANOVA

Table 16. Baseline Characteristics of Participants by Quartiles of Restricted Hours Exercised Per Week

	1st Quartile (≤ 2 hrs) N = 65	2nd Quartile (2-4 hrs) N = 39	3rd Quartile (4-8 hrs) N = 53	4th Quartile (8-34 hrs) N = 48	P value
Mean evaluation age (yr)	86.28 (SD±4.61)	85.77 (SD±4.96)	84.89 (SD±4.66)	84.45 (SD±4.77)	0.1874*
Mean education (yr)	13.57 (SD±2.27)	14.26 (SD±2.23)	14.19 (SD±2.78)	14.00 (SD±2.79)	0.4683*
Mean SES	43.57 (SD±12.19)	48.59 (SD±10.04)	45.69 (SD±12.48)	45.60 (SD±10.95)	0.2098*
Mean follow-up in years	3.73 (SD±2.71)	3.50 (SD±2.31)	4.77 (SD±3.11)	4.10 (SD±3.08)	0.1294*
Mean age at onset (yr)	91.60 (SD±3.86)	89.57 (SD±4.79)	90.63 (SD±4.54)	87.63 (SD±4.51)	0.2176*
Mean baseline MMSE score	28.26 (SD±1.54)	27.90 (SD±1.52)	28.51 (SD±1.30)	27.98 (SD±1.39)	0.1553*
Mean baseline IADL	0.11 (SD±0.31)	0.21 (SD±0.61)	0.04 (SD±0.19)	0.05 (SD±0.2)	0.1113*
SEX					0.1587**
Female	44	25	31	20	
Male	21	14	22	23	
Living					0.0659**
Alone	45	19	32	20	
Not Alone	20	20	21	23	
RACE					
White	56	37	50	38	
Black	6	2	2	4	
Other	3	0	1	1	

** One-way ANOVA
** Chi-square test

Table 17. Frequency of Cognitive Decline According to Physical Activity (Restricted Quartile Values)

	Number of Subjects	Cognitive Impairment	p-value*
Quartiles of Blocks Walked per Week			0.3462
Lowest	55	12	
2nd	63	12	
3rd	52	17	
Highest	32	9	
Quartiles of Hours of Exercise per Week			**0.0059**
Lowest	65	21	
2nd	39	15	
3rd	53	7	
Highest	43	6	

*Chi-square Test

Table 18. Baseline Characteristics of Participants by Leisure Activity Groups

	1st Group (low passive/low active) N = 51	2nd Group (low passive/high active) N = 52	3rd Group (high passive/low active) N = 52	4th Group (high passive/high active) N = 57	P value
Mean evaluation age (yr)	85.74 (SD±4.51)	84.21 (SD±45.66)	86.45 (SD±3.66)	84.74 (SD±4.82)	0.0729*
Mean education (yr)	13.94 (SD±2.61)	13.37 (SD±2.04)	14.15 (SD±2.63)	14.33 (SD±2.77)	0.2365*
Mean SES	46.61 (SD±13.57)	41.47 (SD±12.07)	47.04 (SD±10.35)	46.93 (SD±9.93)	**0.0396***
Mean years of follow-up	3.90 (SD±2.85)	3.92 (SD±2.97)	3.96 (SD±2.73)	4.57 (SD±2.98)	0.5598*
Mean age at onset (yr)	91.34 (SD±4.53)	88.81 (SD±4.70)	90.74 (SD±4.66)	88.56 (SD±4.28)	0.2978*
Mean baseline MMSE score	28.27 (SD±1.42)	27.94 (SD±1.62)	28.29 (SD±1.56)	28.37 (SD±1.17)	0.4430*
Mean baseline IADL	0.08 (SD±0.34)	0.13 (SD±0.48)	0.13 (SD±0.34)	0.04 (SD±0.19)	0.3809*
SEX					0.4581**
Female	31	36	29	32	
Male	20	16	23	25	
Living					0.1568**
Alone	27	34	24	36	
Not Alone	24	18	28	21	
RACE					
White	43	46	48	54	
Black	4	6	2	3	
Other	4	0	2	0	

* One-way ANOVA

** Chi-square test

Table 19. Baseline Performance on Neuropsychological Tests by Leisure Activity Groups

	LP/LA Group[2] N = 51	LP/HA Group[2] N=52	HP/LA Group[2] N = 52	HP/HA Group[2] N = 57	P value[1]
Word Acquisition	18.88 (3.89)	17.92 (3.32)	18.69 (3.86)	18.54 (3.49)	0.5740
Delayed Recall	6.46 (1.83)	5.42 (2.08)	6.13 (1.96)	6.09 (2.00)	0.0607
Animals	17.28 (4.57)	15.56 (4.51)	17.27 (4.76)	17.45 (3.73)	0.0947
Boston Abbreviated	14.19 (0.84)	13.94 (1.09)	14.20 (0.93)	14.10 (1.09)	0.5406
Logical Memory I	11.64 (3.83)	11.83 (3.40)	11.63 (5.36)	11.72 (3.90)	0.9954
Logical memory II	9.50 (4.67)	9.06 (4.67)	9.40 (5.24)	9.21 (4.67)	0.9671

LP/LA = low passive/low active group
LP/HA = low passive/high active group
HP/LA = high passive/low active group
HP/HA = high passive/high active group
[1] One-way ANOVA
[2] Mean (SD)

Table 20. Baseline Characteristics of Participants by Quartiles of Total Activity Points

	1st Quartile (5.50-27 pts.) N = 60	2nd Quartile (27-34 pts.) N = 49	3rd Quartile (34-40.5 pts.) N = 51	4th Quartile (40.5-69.50 pts.) N = 52	P value
Mean evaluation age (yr)	86.17 (SD±4.35)	84.97 (SD±4.62)	85.28 (SD±5.01)	84.51 (SD±5.08)	0.3020*
Mean education (yr)	13.83 (SD±2.59)	13.78 (SD±2.36)	14.24 (SD±2.70)	14.02 (SD±2.56)	0.7940*
Mean SES	45.35 (SD±13.05)	44.41 (SD±12.80)	46.68 (SD±10.55)	45.78 (SD±10.00)	0.8097*
Mean years of follow-up	3.79 (SD±2.64)	3.74 (SD±2.79)	4.56 (SD±3.08)	4.33 (SD±3.01)	0.3785*
Mean age at onset (yr)	91.65 (SD±4.36)	87.87 (SD±4.85)	91.53 (SD±2.94)	87.99 (SD±4.56)	**0.0354***
Mean baseline MMSE score	28.37 (SD±1.46)	27.94 (SD±1.41)	28.12 (SD±1.61)	28.42 (SD±1.29)	0.2923*
Mean baseline IADL	0.07 (SD±0.31)	0.14 (SD±0.5)	0.10 (SD±0.30)	0.08 (SD±0.27)	0.700*
SEX					0.8249**
Female	37	30	28	33	
Male	23	19	23	19	
Living					0.3677**
Alone	33	25	28	35	
Not Alone	27	24	23	17	
RACE					
White	52	44	46	49	
Black	4	3	5	3	
Other	4	2	0	0	

* One-way ANOVA
** Chi-square test

Table 23. Relation Between the Baseline Characteristics and the Time to Cognitive Decline – Results of the Continuous Variable Univariate Cox Analysis

Variable	Pr > Chisq*
Blocks Walked	0.4605
Exercise (hours)	**0.1178**
Total Activity	**0.0274**
Mini Mental State Examination	**0.0152**
Evaluation Age	**0.0002**
Word Acquisition	**0.0021**
Delayed Recall	**0.0002**
Animals	**0.0378**
Socioeconomic Status	0.9426
Education	0.6668
Independent Activities of Daily Living	0.1706
Logical Memory I	0.3926
Logical Memory II	0.3277
Boston Abbreviated	0.2979
Steps per Second	0.5307
Modified Cumulative Illness Rating Scale	**0.0891**

* P values < 0.15 are highlighted and considered statistically significant

Table 24. Variables Included in the Multivariate Analysis of the Association Between Participation in the Baseline Leisure Activities and Time until Progression to Cognitive Decline

Variable
Mini Mental State Examination
Evaluation Age
APOE allele 4 Status
Word Acquisition
Delayed Recall
Animals
OBAS Cohort Indicator Variable
DPS Cohort Indicator Variable
Exercise Group
Activity0 Group (Low/Low group vs. all others together)
Total Activity

Table 25a. Preliminary[1,2] Multivariate Cox Proportional Hazards Model I

Variable	HR	95% HR CI
Evaluation Age	1.080	(1.016, 1.148)
APOE allele 4 Status	2.128	(1.130, 4.008)
Delayed Recall Test	0.761	(0.654, 0.884)
Exercise Group	0.314	(0.161, 0.613)

[1] Preliminary Cox Model I was developed using all study participants regardless of availability of their Modified Cumulative Illness Rating Scale (MCIRS) scores. The variable MCIRS itself was not included in this model.

[2] Preliminary Cox Model I does not include interactions or adjustment for the important confounders sex and education.

Table 25b. Multivariate Cox Proportional Hazards Model I[1,2]

Variable	HR	95% HR CI
Evaluation Age	1.097	(1.029, 1.169)
APOE allele 4 Status	2.264	(1.195, 4.289)
Delayed Recall Test	0.750	(0.645, 0.872)
Exercise Group	0.308	(0.158, 0.600)
Sex	0.587	(0.314, 1.097)
Education	0.996	(0.880, 1.128)

[1] Cox Model I was developed using all study participants regardless of availability of their Modified Cumulative Illness Rating Scale (MCIRS) scores. The variable MCIRS itself was not included in this model.

[2] Cox Model I was evaluated for the interactions and adjusted for the important confounders sex and education.

Table 26a. Preliminary[1,2] Multivariate Cox Proportional Hazards Model II

Variable	HR	95% HR CI
Evaluation Age	0.984	(0.846, 1.145)
APOE allele 4 Status	3.196	(1.222, 8.356)
Delayed Recall Test	0.748	(0.593, 0.943)
Exercise Group	0.283	(0.098, 0.814)

[1] Preliminary Cox Model II was fitted using only those participants for whom the Modified Cumulative Illness Rating Scale (MCIRS) scores were available (complete case analysis).
[2] Preliminary Cox Model II does not include interactions or adjustment for the important confounders sex and education.

Table 26b. Preliminary[1,2] Multivariate Cox Proportional Hazards Model II (Interaction Terms Included)

Variable	HR	95% HR CI
Evaluation Age	0.943	(0.801, 1.111)
APOE allele 4 Status	2.843	(1.071, 7.545)
Delayed Recall Test	0.762	(0.608, 0.955)
Exercise Group	0.295	(0.101, 0.859)
Evaluation Age* OBAS	1.015	(1.001, 1.030)

[1] Preliminary Cox Model II was fitted using only those participants for whom the Modified Cumulative Illness Rating Scale (MCIRS) scores were available (complete case analysis).
[2] Preliminary Cox Model II has been evaluated for the interactions, but it does not include adjustment for the important confounders sex and education.

Table 26c. Multivariate Cox Proportional Hazards Model II[1,2]

Variable	HR	95% HR CI
Evaluation Age	0.951	(0.802, 1.128)
APOE allele 4 Status	2.370	(0.844, 6.654)
Delayed Recall Test	0.721	(0.564, 0.922)
Exercise Group	0.383	(0.123, 1.190)
Evaluation Age* OBAS	1.019	(1.003, 1.034)
Sex	0.868	(0.284, 2.648)
Education	0.853	(0.672, 1.084)

[1] Cox Model II was fitted using only those participants for whom the Modified Cumulative Illness Rating Scale (MCIRS) scores were available (complete case analysis).
[2] Cox Model II has been evaluated for the interactions and adjusted for the important confounders sex and education.

Table 27. Linear Regression Model for The Multiple Imputation[1] – List of the Variables Available for the Model Building and Analysis

Variable
OBAS Cohort Indicator Variable
Socioeconomic Status
Evaluation Age
Place of Residence
Mini Mental State Examination Score
Independent Activities of Daily Living
Delayed Recall Test
Verbal Fluency Test - Animals
Blocks Walked
Gait (steps per second)
Follow-up (years)
Ethnicity
Logical Memory I Test
Cognitive Status (impaired vs. intact)
Sex
APOE allele 4 Status
Indicator Variable for Living Arrangements (alone/not alone)
Exercise (hours)
Total Activity

[1] Model for prediction of the missing Modified Cumulative Illness Rating Scale (MCIRS) values from the other variables in the data set

Table 28. Linear Regression Model for the Multiple Imputation[1] – Summary of the Simple Linear Regression Analysis[2]

SLR Variable Selection	SLR P-value
OBAS Cohort Indicator Variable	<0.0001
Evaluation Age	0.0851
Place of Residence (home vs. retirement community)	0.1803
Independent activities of Daily Living	0.0010
Delayed Recall Test	0.0023
Verbal Fluency Test – Animals	0.1290
Gait (steps per second)	0.1827
Follow-up (years)	0.0194
Ethnicity (white, black, other)	0.1538
Cognitive Status (impaired vs. intact)	0.0021
APOE allele 4 Status	0.0945
Exercise (hours)	0.0778

[1] Model for prediction of the missing Modified Cumulative Illness Rating Scale (MCIRS) values from the other variables in the data set

[2] Simple Linear Regression conducted to select significant variables for the inclusion into the Multiple Linear Regression Model for the Multiple Imputation

Table 29a. Multiple Linear Regression Model for the Prediction of the Missing Modified Cumulative Illness Rating Scale (MCIRS) Values

Variable	Parameter Estimate	Standard Error	Pr > |t|
Intercept	16.6060	1.4470	<0.0001
OBAS Indicator Variable	-3.3680	0.6444	<0.0001
Place of Residence Indicator Variable	1.7292	0.7551	0.0237
IADL	3.6705	0.9501	0.0002
Delayed Recall Test	0.2889	0.1448	0.0482
Animals Test	0.1079	0.0667	0.1084
Exercise	-0.0593	0.0448	0.1884

Figure 1a. The Normal Probability Plot

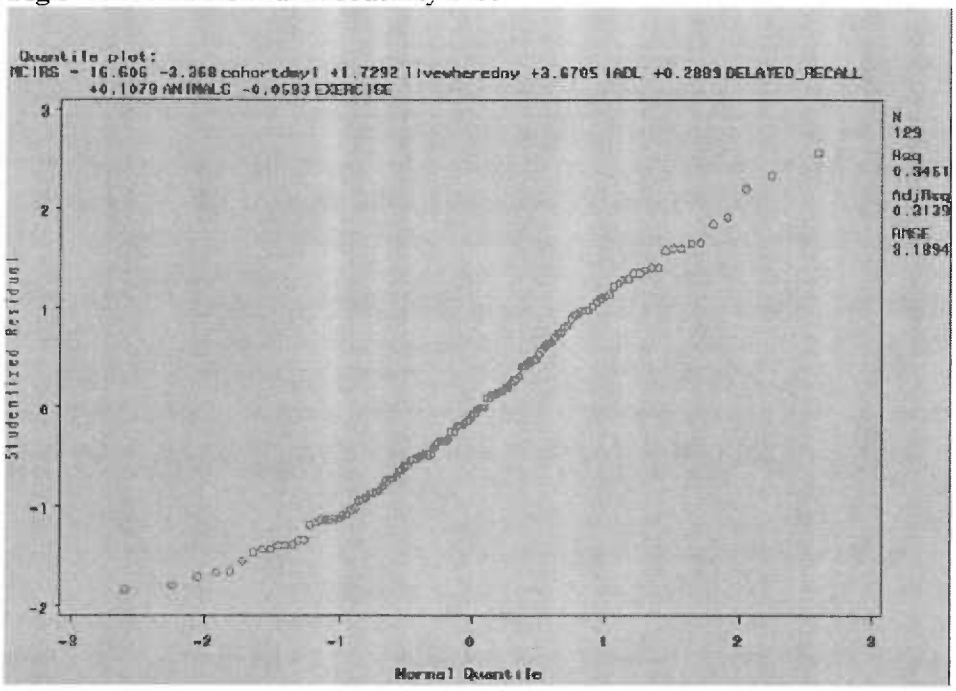

Figure 1b. Plot of Studentized Residuals Against Predicted Values

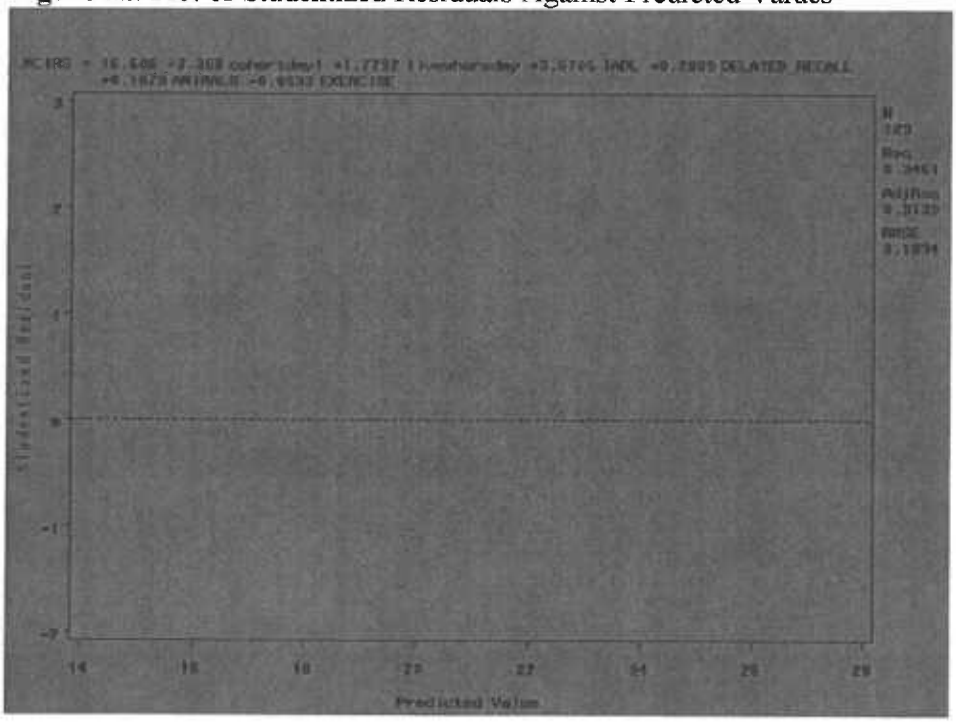

Table 29b. Preliminary[1] Cox Proportional Hazards Model III – Model Including Imputed Modified Cumulative Illness Rating Scale (MCIRS) Variable

Variable	HR	95% HR CI
MCIRS	0.943	(0.781, 1.139)
Evaluation age	1.081	(1.009, 1.159)
APOE allele 4 Status	2.230	(1.045, 4.761)
Delayed Recall	0.765	(0.644, 0.909)
Exercise group	0.298	(0.134, 0.664)

[1] Preliminary Cox Model III does not include interactions or adjustment for the important confounders sex and education.

Table 29c. Final[1] Cox Proportional Hazards Model III – Model Including Imputed Modified Cumulative Illness Rating Scale (MCIRS) Variable

Variable	HR	95% HR CI
MCIRS	0.942	(0.778, 1.141)
Evaluation age	1.098	(1.020, 1.182)
APOE allele 4 Status	2.407	(1.123, 5.160)
Delayed Recall Test	0.756	(0.635, 0.901)
Exercise group	0.294	(0.131, 0.660)
Sex	0.563	(0.270, 1.171)
Education	0.990	(0.857, 1.144)

[1] Final Cox Model III was evaluated for the interactions and adjusted for the important confounders sex and education.

Table 30. Multivariate Cox Proportional Hazards Models Summary[1]

Variable	HR	95% HR CI
COX MODEL I[2]		
Evaluation Age	1.097	(1.029, 1.169)
APOE allele4 Status	2.264	(1.195, 4.289)
Delayed Recall Test	0.750	**(0.645, 0.872)**
Exercise Group	0.308	**(0.158, 0.600)**
Sex	0.587	(0.314, 1.097)
Education	0.996	(0.880, 1.128)
COX MODEL II[3]		
Evaluation Age	0.951	(0.802, 1.128)
APOE allele 4 Status	2.370	(0.844, 6.654)
Delayed Recall Test	0.721	**(0.564, 0.922)**
Exercise Group	0.383	(0.123, 1.190)
Evaluation Age * OBAS	1.019	(1.003, 1.034)
Sex	0.868	(0.284, 2.648)
Education	0.853	(0.672, 1.084)
COX MODEL III[4]		
MCIRS	0.942	(0.778, 1.141)
Evaluation age	1.098	(1.020, 1.182)
APOE allele 4 Status	2.407	(1.123, 5.160)
Delayed Recall	0.756	**(0.635, 0.901)**
Exercise group	0.294	**(0.131, 0.660)**
Sex	0.563	(0.270, 1.171)
Education	0.990	(0.857, 1.144)

[1] Models evaluated for the interactions and adjusted for the important confounders sex and education.
[2] Cox Model I was developed using all study participants regardless of availability of their Modified Cumulative Illness Rating Scale (MCIRS) scores. The variable MCIRS itself was not included in this model.
[3] Cox Model II was fitted using only those participants for whom the Modified Cumulative Illness Rating Scale (MCIRS) scores were available (complete case analysis).
[4] Cox Model III includes imputed Modified Cumulative Illness Rating Scale (MCIRS) variable

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APPENDIX

OBAS Subject Selection Criteria

Requirements for Entry	Major Exclusion Criteria
Principal Language: English	Medical conditions
Rudimentary Reading and Writing Skills	Diabetes mellitus
Functionally Independent	Hypertension (supine blood pressure > 160/95)
Gives Informed Consent	Angina pectoris
Willing and able to return for follow-up	Cardiac arrhythmia
Willing to discuss brain autopsy	Myocardial infraction
Has not sought evaluation for cognitive impairment	Stroke/transient ischemic attack
Score = 0 on Clinical Dementia Rating Scale	Chronic pulmonary disease
Score ≥24 on Mini-Mental State Examination	Chronic renal disease
Score ≤11 on Geriatric Depression Scale	Chronic immunosuppression
Score ≤10 on Cornell Depression Scale	Untreated hypothyroidism
Score ≤12 on Instrumental Activities of Daily Living	Syphilis
	Vitamin deficiencies
	Seizure disorders
	Active cancer (≤t years no recurrence)
	Parkinson's disease
	Major surgeries
	Coronary bypass
	Carotid endarterectomy
	Psychiatric disorders
	Chronic schizophrenia
	Major affective disorders
	Phobias
	Chronic anxiety
	Vision and hearing
	Vision uncorrectable to 20/100 OU
	Hearing loss (interferes with speech perception)
	Other conditions
	Alcohol or drug abuse
	Significant head injury (>30 min unconscious)
	Unexplained prolonged loss of consciousness
	Use of medications impairing cognitive function

DPS Subject Selection Criteria

DEMENTIA PREVENTION STUDY OF GBE IN THE OLDEST OLD

For Office Use Only

Clinic Site | Subject ID# | Subject Designation | Evaluation #

Subject Name _____ **Medical Record #** _____

Evaluation Date M D Y **Evaluating Researcher** _____

Oregon Health Sciences University Aging and Alzheimer's Disease Center
Center for Complimentary and Alternative Medicine in Neurologic Disorders
Inclusion Criteria Checklist

CLINICIAN REVIEWED:

- ❑ **SCHEDULE V1**
- ❑ **ALL INCLUSION CRITERIA MET—ENROLL; SCHEDULE V2**
- ❑ **EXCLUDED** reason: _____
  - ❑ Send information about CBDP, other studies

INCLUSION CRITERIA: *(if not met, circle and further explain)*

- ❑ 1. **Age > 85 years**
- ❑ 2. No **complaint of memory** inpairment compared to others their age.
- ❑ 3. Has **not sought assessment** for memory or cognitive dysfunction.
- ❑ 4. **Blessed** score < 12
- ❑ 5. **Telephone Screening Interview** Completed
- ❑ 6. Sufficient **English language** skills to complete all testing
- ❑ 7. Available **informant** with frequent contact (at least one hour per day, three days a week)
- ❑ 8. Functionally **independent**
- ❑ 9. Sufficient **vision and hearing** to complete all testing
- ❑ 10. Normal Memory function defined by an education-adjusted score on **LM-II (WMS-R)**
  - >8 for 16 or more years of education
  - >4 for 8-15 years of education
  - >2 for 0-7 years of education
- ❑ 11. **Mini-Mental** State Examination score > 23
- ❑ 12. **CDR** = 0
- ❑ 13. **CESD 10** < 4
- ❑ 14. **General health status** that will not interfere with ability to complete longitudinal study
- ❑ 15. NO **diseases associated with dementia** such as AD, *ischemic vascular dementia, normal pressure hydrocephalus*, or *Parkinson's disease*

  Explain: _____
- ❑ 16. NO significant **disease of the CNS** such as *brain tumor, seizure disorder, subdural hematoma, cranial arteritis*

  Explain: _____

DPS Subject Selection Criteria, continued

Subject Initials: _____

- ❑ 17. NO current (within last 2 years) **alcohol or substance abuse** according to DSM IV criteria
- ❑ 18. NO major *depression, schizophrenia*, other major **psychiatric disorder** (DSM IV)
- ❑ 19. Normal **laboratory values;** no indictation of *B12 deficiency, thyroid disease*

  Explain: _____
- ❑ 20. NO untable or symptomatic **cardiovascular disease** such as *coronary artery disease* with frequent angina, or congestive heard failure with *shortness of breath* at rest

  Explain: _____
- ❑ 21. NO **insulin dependent** *diabetes* mellitus

  Explain: _____
- ❑ 22. NO active **systemic cancer** within 5 years of study entry. Gleason Grade < 3 prostate cancer, and non-metastatic cancers are acceptable

  Explain: _____
- ❑ 23. NO **bleeding problems**; no use of *Coumadin/Warafin* or similar
- ❑ 24. NO illness that requires **> 1 visit per month to a clinician**

  Explain: _____
- ❑ 25. NO significant, progressive **vision loss** (severe *macular degeneration*)

  Explain: _____
- ❑ 26. NO need for **oxygen supplementation** for adequate function
- ❑ 27. NONE of the following **medications:**
  - △ a. Frequent use of high doses of *analgesics*
  - △ b. *Sedative medications* except for those used occasionally for sleep (use limited to no more than twice per week)
  - △ c. Subjects may be on doses of CNS-active medications that have been stable for at least 2 months including *cimetidine, beta-blockers* and *selective serotonin reuptake inhibitors*
  - △ d. Subjects taking *neuroleptics, antiparkinsonan* agents, *systemic corticosteroids*, and *narcotic analgesics* will be excluded. In the case where these were used for a self-limited time, they must have been discontinued for 5 half-lives prior to baseline.
  - △ e. Subjects will not be excluded for use of *over-the-counter supplements*, but the dose must not be changed during the course of the trial unless medically indicated.
  - △ F. *Cholinesterase inhibitors*
  - △ G. Use of *investigational drugs* within 5 half-lives prior to baseline
  - △ H. Use of *Coumadin; Warafin*; or other for bleeding complications
  - ❑ QUESTIONABLE MEDICATIONS (indicate clinician response)
    - _____
    - _____
    - _____
    - _____
    - _____

NOTES: _____

_____

AADAPt Subject Selection Criteria

Inclusion Criteria

1) Self-reported African-American residing in Portland metropolitan area
2) Age >65 years, of either gender
3) Ambulatory
4) Adequate vision, hearing and language abilities to understand consent, and complete assessments
5) Available collateral historian
6) Gives informed consent

Exclusion Criteria

1) Dementia as defined by Clinical Dementia Rating score <0.5
2) Unstable and/or untreated medical or psychiatric illness
    a. Potential or enrolled subjects, who are found to have such illness, including harmful alcohol or drug use or disorders, will be referred to their primary care physician (PCP)
    b. Individuals referred to their PCP for such reasons may remain enrolled in the present study, if this is deemed safe for the participant, at the discretion of the investigators.
    c. For those not initially enrolled, reassessment is possible, once the condition has stabilized and/or is being appropriately treated.
    d. Individuals requiring, but refusing referral will be dropped from the study.
    e. Individuals without a PCP or medical insurance will be offered assistance in obtaining such.
3) Any subject who, in the opinion of the investigator, is unlikely to comply with or be able to complete the study protocol
4) Does not meet one or more inclusion criteria

Modified Cumulative Illness Scale (MCIRS)

ADCO

Modified Cumulative Illness Rating Scale

Office Use Only

Clinic Site | Patient ID# | Patient Designation | Evaluation #

Patient Name _____ Medical Record # _____

Evaluation Date ___ (M) ___ (D) ___ (Y) Evaluating Clinician _____

Name of Person Completing Form _____ Date Completed _____

1 = NONE:	No impairment to that organ/system
2 = MILD:	Impairment does not interfere with normal activity; treatment may or may not be required; prognosis is excellent. (Examples could be skin lesions, hernias, or hemorrhoids.)
3 = MODERATE:	Impairment interferes with normal activity; treatment is needed; prognosis is good. (Examples could be gallstones, diabetes, or fractures.)
4 = SEVERE:	Impairment is disabling; treatment is urgently needed; prognosis is guarded. (Examples could be resectable carcinoma, pulmonary emphysema, or congestive heart failure.)
5 = EXTREMELY SEVERE:	Impairment is life threatening; treatment is urgent or of no avail; prognosis is grave. (Examples could be myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, or embolus.)

_____ 1. **Cardiac** (heart only)

_____ 2. **Hypertension** (rating is based on severity; affected systems are rated separately)

_____ 3. **Vascular** (blood, blood vessels and cells, marrow, spleen, lymphatics)

_____ 4. **Respiratory** (lungs, bronchi, trachea below the larynx)

_____ 5. **EENT** (eye, ear, nose, throat, larynx)

_____ 6. **Upper GI** (esophagus, stomach, duodenum, biliary and pancreatic trees; do not include diabetes)

_____ 7. **Lower GI** (intestines, hernias)

_____ 8. **Hepatic** (liver only)

_____ 9. **Renal** (kidneys only)

_____ 10. **Other GU** (ureters, bladder, urethra, prostate, genitals)

_____ 11. **Musculo-Skeletal-Integumentary** (muscles, bone, skin)

_____ 12. **Neurological** (brain, spinal cord, nerves; do not include dementia)

_____ 13. **Endocrine-Metabolic** (includes diabetes, diffuse infections, infections, toxicity)

_____ 14. **Psychiatric/ Behavioral** (includes dementia, depression, anxiety, agitation, psychosis)

_____ **TOTAL**

ADCO-MCIRS 4/17/96