STUDY PROTOCOL

A randomized control trial on the effects of physical exercise on cognitive function in elderly women with aMCI

Adam Slotnick

Background and rationale

Cases of neurodegenerative diseases are expected to rapidly increase as Baby Boomers retire. Some of the most debilitating of these diseases affect cognitive functioning and daily activities. Consequently, the economic costs associated with treating and caring for affected individuals is also set to increase substantially. The monetary costs associated with Alzheimer’s disease (AD) alone are expected to reach $1 trillion in the United States by mid-century. AD affects women more frequently than men. Individuals with AD and other dementias first suffer from mild cognitive impairment.

Cognitive functioning declines with age. The continuum begins with normal cognitive functioning, transitions to Mild Cognitive Impairment (MCI) and ends with dementia. Many factors affect an individual’s chances of developing cognitive impairment faster than others. Risk factors for AD include genetic perceptibility (apolipoprotein epsilon 4 allele) and lifestyle factors (eg., developing Type II diabetes as a consequence of obesity). MCI, also known as prodromal AD, indicates the beginning of cognitive decline. Cognitive impairment affects many domains, including memory, language and executive function. A patient is described as suffering from amnestic Mild Cognitive Impairment (aMCI) if memory is their only impairment (Petersen
2004). MCI is classified first as amnestic or non-amnestic based on memory impairment, and then as either single or multiple domain.

Cognitive functioning is assessed using standardized cognition diagnostic tests. The Mini-Mental State Examination (MMSE) is one of the most commonly used tools for screening cognitive impairment and dementia. The test consists of eleven questions involving memory recall and language skills. Respondents’ scores are graded on a scale, with a maximum possible score of 30 points. The cut-point for impairment is affected by age and education. Median scores begin to decline in adulthood for some and across all education levels at age 70. Scores for those with an elementary education are noticeably lower (Crum 1993, O’Bryant 2008, Stein 2012). A recent analysis of diagnostic tests for evaluating dementia and MCI revealed that the MMSE has a moderate Cohen’s d for MCI versus no dementia of .69 (Larner 2014).

Physical exercise is recommended for people of all ages. It is a powerful preventive tool against illness and disease. Exercise is beneficial not only for cardiovascular health (Ho 2012), but also cognitive functioning. Aerobic exercise, such as running and cycling, benefits heart and mental health. Resistance training (eg., using weights or resistance tubing) is beneficial for strengthening the musculoskeletal system. The development of lean muscle mass is also important as muscles begin to atrophy as early as age 30. The benefits of exercise in old age cannot be underscored. Both aerobic and resistance training are important for health during the life course.

**Methods & Design**

This efficacy behavioral trial uses a 2x2 factorial design. Aerobic exercise is the primary intervention and resistance training is the secondary intervention. To the author’s knowledge,
this is the first randomized clinical trial to utilize a factorial design to assess the effect of these specific interventions on women with MCI, dementia or AD. This study is feasible based on previous studies and the current setting. A review of the economic costs of aerobic and resistance training in the elderly (EXCEL clinical trial) found that both reduce economic costs in comparison to standard care (Davis 2013).

Setting

The Sunny Valley Retirement Community is a residential property for retirees in Happy Valley, Florida. More than 3,000, largely middle-class residents, reside in this 65 and over condominium community. Residents have access to leisure facilities, including tennis courts, two golf courses and a facility with exercise equipment similar to a commercial gym. This gym has a professional staff, including personal trainers.

Intervention activities

Exercise is a behavioral intervention used in clinical trials. Participants in previous studies exercised either twice (Suzuki 2012) or three times per week (Scherder 2005, Yoon 2013). This number needs to be even in the present trial given the combined treatment group. Two workouts per week compared to four are reasonable given the ages of participants. Participants in the current study will exercise twice per week. The aerobic training (AT) primary intervention group will use either a treadmill or recumbent bicycle for thirty minutes twice per week. The secondary intervention resistance training (RT) group will train for thirty minutes twice per week. The combined interventions, aerobic and resistance training (ART) group, will participate in one session of each intervention, for two total weekly sessions A stretching and relax (ST) group will act as the standard treatment control (Uni. Brit. Col. 2014, USAMRMC
2014). The activities in this group will consist of twice weekly thirty minute sessions. Previous research shows benefits for mild/moderate exercise and its effects on aging versus light or vigorous exercise. The Mayo Clinic Study of Aging cohort reported an Odds Ratio of .6 (.43-.88 95% confidence interval) in midlife and .68 (.49-.93 95% confidence interval) for late life. Moderate exercise was associated with lowered odds of developing MCI (Geda 2010). An RCT on mild exercise in the very old (mean age of 86) showed promise, but only had a 43 person sample size. In the current study, all participants will be supervised by a professional trainer who tailors a suitable plan for each individual consistent with the trial’s guidelines for mild exercise.

**Objectives**

The objective of this study is to assess the impact of the exercise interventions on cognitive function. The mean MMSE score is expected to be greater in the single intervention groups (AT and RT) when compared to the standard treatment, with the largest mean difference expected among the combined intervention group (ART). The effectiveness of the interventions will be tested with the aim of translating research results into public health practice.

**Study endpoints**

The estimated study start date is January 1, 2015. Previous exercise trials ranged from brief (6 and 12 weeks) to lengthy (12 or 24 months). The current trial will last six months. This time period allows sufficient time for the body to adapt to physiological changes associated with physical exercise, while taking cost considerations into account. In addition to baseline testing of both outcomes, follow up testing will occur at two month intervals. The primary research outcome will examine cognitive function using the MMSE. The secondary outcome measure is
an improvement in physical fitness. A 400 meter fast walk will be used to test fitness levels (Hasselbalch 2014).

**Eligibility criteria**

The current study is open to women ages 70 through 79. This is a lower age range than the previous trials noted above. It is important to introduce physical exercise to those who are inactive in order to prevent possible future cognitive deterioration. Participants will be screened by the MMSE, and must score ≥ 21 to 27 points, with adjustments made for age and education level. This cut-point is based on analysis of Crum et al.’s MMSE norms and is consistent with similar studies. Additionally, participants must have subjective memory complaints as registered by a medically trained interviewer. Their Body Mass Index (BMI) must fall from 18.5 to 30 (healthy weight and overweight) and have physician approval to participate.

Any women diagnosed with a neurodegenerative disease, such as a dementia diagnosis will be excluded. A history or current psychiatric condition will exclude a potential participant. The other exclusion criteria are: stroke history; orthopedic or musculoskeletal problems; a diabetes diagnosis (Type I or Type II); individuals who are underweight (BMI <18.5) or obese (BMI >30); and those who are currently engaged in the types of physical activity being studied (Uni. Brit. Col. 2014, USAMRMC 2014). Additionally, residents who migrate during the seasons (snowbirds) will be excluded.

**Dealing with loss to follow-up**

It is crucial to minimize the chances of participants leaving the trial before its conclusion and the loss of data. The exclusion criteria works to minimize part of this loss by limiting participants who are not fit for engaging in the type of exercise included in this trial. People who migrate are also excluded. Nonetheless, participants may relocate, drop out due to injury or die
(from an unrelated issue) during the trial. Missing values will be accounted for using multiple
imputation in SAS statistical software (SAS Institute Inc, Cary, NC). All participants will be
analyzed using the intent-to-treat protocol (ITT). Similar trials on physical activity in seniors
used ITT to deal with missing data (Lautenschlager 2008, Suzuki 2012). ITT allows for analysis
in line with this researcher’s preference for conservative methods. There are no stopping rules in
place since the exercise interventions should benefit the participants and the exclusion criteria
aimed for a reduction in the chance of individuals experiencing adverse effects.

**Sample size and power**

The sample size and power calculations for this trial are based on the MMSE scores. This
is in line with standard procedures, in which the power calculations are based on the primary
outcome variable (Peduzzi 2002). The sample size for this trial is inflated to allow for possible
loss of participants during the course of this trial. Similarly conducted trials reported: an AD trial
\( (n=354, 12 \text{ months}) \) had a less than 10% loss (Barnes 2005), an AD trial \( (n=170, 18 \text{ months}) \) had
an 18.8% loss (Lautenschlager 2008) and an aMCI trial \( (n=50, 12 \text{ months}) \) lost 6% to follow up,
with a 79.2% adherence rate (Suzuki 2012). The researcher of the current trial decided to create a
larger sample size to reflect a potential 20% participant loss rate. This is a conservative number
given that this trial has a shorter duration, six months, compared to the trials described above.

The initial sample size calculation (without adjusting for loss) is based on a two sample t-
test for mean difference of .9, with 80% power and a standard deviation of 2. The standard
deviceation is derived from an analysis of population based norms for the MMSE (Crum 1993).
While another analysis pegged the standard deviation at 3 (Soubelete 2011), Crum et al. studied
results from 18,056 people stratified by age and education. The standard deviation for 70-74 and
75-79 year olds was 1.8 and 2.1, respectively. The numbers are 1.5 to 1.6 for those with at least
nine years of education. Since education and income tend to be linked, it is possible to make power calculations based on a lower standard deviation. The mean scores are 27 for those with high school experience and 28 for those with college experience. Sex based comparisons are not included. A Japanese study similar to the current trial reported baseline MMSE scores of 26.8±1.8 (n=25) for the treatment group and 26.6±1.6 (n=25) for the control group (Suzuki 2012). I chose the higher standard deviation number of 2 (compared to 1.6) due to the inclusion criteria of MMSE scores lower than the mean data provided in the Crum and Suzuki studies. The preference is to choose conservative estimates.

The next step was to determine the mean difference and number of participants. The researcher’s goal was to choose a higher number of participants than anticipated for a given effect size to account for as high as a 20% decline in sample size due to attrition or data loss. The trial most similar to this study protocol had an MMSE mean difference between the sole intervention and the control group of 1.69 at the six month follow up, and .91 at the study’s conclusion (Suzuki 2012). The authors do not discuss their power calculations. Based on the numbers presented in their paper, the study had an anemic 45.8% power at a mean difference of .91 compared with 93.1% power at a 1.69 difference. Furthermore, there is no discussion of the dramatic increase in MMSE score for the control group in the second half of the study, while the intervention group shows a decrease. The protocol’s author believes that the information provided by the completed trial can serve only as a guide at best. The 26.7 baseline mean MMSE score in the study is at the upper limits of the protocol’s inclusion criteria. It is likely that the inclusion of people in the current trial with lower baseline scores may register larger changes in cognition scores during the trial. However, given the relatively short six month duration, it is
likely that a larger sample size will be needed to detect a small mean score change. The goal is to be conservative in order to detect a .9 mean difference after accounting for a 20 percent loss.

The result of the power calculation is the need for 57 women per intervention, or 228 in total. Adjusting for the potential loss of 20 percent of the original participants results in the need for 72 per intervention, or 288 women in total. The initial sample size will provide the study with 88.4 percent power (see Appendix Figures 1 and 2). The calculated Cohen’s d results in a moderate effect size of .529.

**Randomization and blinding**

The 288 participants will be randomly assigned to one of the four study groups. The block randomization was performed using SAS 9.3 (SAS Institute Inc, Cary, NC) (see Appendix Figure 2). Four women were grouped to one of 72 blocks. Each participant was then randomly assigned to one of the four treatment groups. The participant flow is shown in Appendix Figure 4. There is limited masking. The ST group will not be made aware that they are members of the control group. This will work to prevent a lack of enthusiasm among participants in this group. Additionally, data analysts will initially be blinded to the data they are working with.

**Data analysis plan**

The objective of the analysis is to determine the effect of the interventions on cognitive scores. Additionally, it is hypothesized that the combined treatment group will have a greater effect than either of the single interventions. The treatments will be evaluated using an independent samples t-test with an alpha of .05 which is in line with the methodology used in behavioral trials (Scherder 2005, Suzuki 2012), particularly a factorial (Lewycka 2010). The baseline demographic characteristics are age, education level, marital status, ethnicity and asset
level (rather than income, for retirees). These characteristics will be included in the analysis (Peduzzi 2002). The secondary outcome data for the fitness test will also be assessed in this manner, but separate from the primary outcome. This is why the sample size calculation only took the primary outcome into consideration (Marras 2004). Similar to other factorial trials, the present study will be underpowered to detect the interaction effect of the combined treatments compared with either the primary or secondary treatment alone (Lewycka 2010). The ITT protocol described previously will be included.

The primary outcome data will be checked for the model assumptions of linearity, normality and constancy of variance. Population MMSE scores have a negatively skewed distribution, including among the elderly (Castro-Costa 2008). This skewness may not occur within the sample data, though, since there is a limited score range for the inclusion criteria. If necessary, the data will be transformed to resemble a normal distribution of data. The longitudinal nature of this factorial trial with repeated measurements will result in the use of a linear mixed effects model. This model was previously used in similar trials (Barnes 2005, Lautenschlager 2008). This will be performed using the MIXED procedure in SAS (SAS Institute Inc, Cary, NC). The participant and time interactions will be included as fixed components (Suzuki 2012). The model is anticipated to include the baseline score and demographic covariates.

**Conclusion**

Physical exercise is one strategy for slowing down the progression of dementia. The demands for care and costs associated with individuals with dementia should gain more attention over the next few decades. Research funding remains scarce even though there is no cure, while the prevalence rises. This study protocol aims to investigate if one or more types of physical
exercise will have a positive effect on participants’ scores on the Mini-Mental State Examination. The study examines affluent female retirees in Florida. Their selection is due to the fact that women have higher rates of longevity compared to men, and affluent individuals also tend to live longer. Additionally, similar studies over the past few years have been conducted abroad (e.g., Australia, Canada and Japan). However, the external validity of this study will be limited. Nonetheless, potential gains seen by this studies participants can serve as a guide for more well-funded future studies with more participants and greater power. Florida may well prove to be the epicenter of dementia research moving forward as long as seniors continue to seek retirement in the Sunshine State.
References


Appendix

\texttt{proc power;}
\texttt{twosamplemeans test = diff meandiff = .9 stddev = 1.7 power = .80 npерgroup = . ; run;}

\begin{figure}[h]
\centering
\includegraphics[width=0.4\textwidth]{sas_power_output.png}
\caption{The goal of the first power calculation was to determine the necessary sample size, before adjusting for potential participant loss, with a mean difference of .9, 80\% power and a standard deviation of 2. This results in the need of 57 participants per intervention.}
\end{figure}

\texttt{proc power;}
\texttt{twosamplemeans test = diff meandiff = .9 stddev = 1.7 power = . npерgroup = 72 ; run;}

\texttt{run;}
Figure 2: The second power calculation reflects the new sample size of 72 participants per intervention, preceding the potential loss of participants.

```sas
title "Treatment Randomization Plan";
proc plan seed=18;
factors Block=72 ordered Subject=4 ordered /noprint;
treatments Treatment=4 random;
output out=RCT
treatment cvals=('AT' 'RT' 'ART' 'ST');
run;
```

```sas
proc print data=RCT noobs;
var block subject treatment;
format subject z3.;
run;
```

Figure 3: The randomization procedure. The first two blocks are shown in the block randomization plan used to assign treatments to the subjects.
Figure 4: Participant flow.