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Abstract

There is growing interest in the potential of exercise interventions in therapy for individuals with Alzheimer's disease (AD). This paper replicates and extends upon some of the analysis of a randomized controlled pilot study that investigates the effect of a 26-week aerobic exercise program on memory, executive function, functional ability, and depression in 68 participants who were likely to develop AD. The replication was focused specifically on the analysis performed on the Memory Composite outcome variable, reproducing an interaction model between two of the main variables, Treatment Arm (Stretching and Toning Exercise versus Aerobic Exercise) and Timepoint (Baseline, Week 13, Week 26). The replication yielded the same values as the original study with similarly insignificant p-values. Using RStudio, the present study tests three additional interaction models, the interaction between Sex and Treatment Arm, between Sex and Timepoint, and between Sex, Treatment Arm, and Timepoint. These tests yielded insignificant p-values, implying that, contrary to the previous literature on gender differences in AD and exercise interventions, gender may not be a differentiating factor in memory. The hypothesis was that the exercise type affects the interaction between time and memory loss in early AD patients.

Key terms: Alzheimer's Disease, exercise intervention, time, memory, gender

Introduction

Alzheimer's disease (AD) is a serious condition that affects 5.8 million Americans. More specifically, 1 in 10 people aged 65 years or over in the United States has been diagnosed with this neurodegenerative disease, with 81% of the population with Alzheimer's being 75 years or older and almost two-thirds being women (Alzheimer's Association, 2019). We hypothesised that the type of exercise (stretching and toning versus aerobic exercise) influences the normal, expected interaction between time and memory loss in individuals likely to develop AD. and that there would be a significant difference ($p < 0.05$) between genders for Memory Composite score across across both types of exercise, and at different timepoints.

Symptoms of AD

Some major symptoms of Alzheimer's that can lead to dementia further down the road are memory loss and confusion, along with physical brain changes that can serve as markers for progression, including loss of hippocampal volume and gray matter volume. One of the earliest psychological signs of AD is short-term memory loss of recently learned information. Deficits in problem solving ability, confusion with time and place, behavioral changes, language difficulties, disorientation, and poor judgment are all signs of the early stages of AD ("10 Early Signs and Symptoms of Alzheimer's"). In addition, symptoms of depression and drastic changes in mood and personality are detected in patients with AD. In the later stages of AD, there is a greater risk of catching infections such as pneumonia, a complete loss of the ability to communicate, and overall, a need for 24-hour assistance for simple, daily tasks ("6 Health Ailments That Accompany Alzheimer's").

Treatments for AD

There is no current cure for the disease; there exist only treatments for some of the symptoms, such as cognition-enhancing medications that target the secondary symptoms of depression and hallucinations.

An alternative that many individuals with AD have turned to is physical exercise, which may slow down some of the psychological symptoms of AD. Since there is a correlation between enhanced cognitive performance and strenuous exercise in athletes, further research has been conducted on the possible benefits of physical activity for those with cognitive decline, specifically people with AD (Hogervorst et. al, 1996).

Current Literature on Exercise and Cognitive Function

Prior research has also been conducted with human participants that demonstrated an increase in cognitive performance after exercise. For instance, a study of healthy, non-AD individuals that tested the effect of high intensity exercise on psychomotor and cognitive ability, found an increase in the speed of performance on the simple reaction time (RT), finger-tapping, and Stroop tests (Hogervorst et. al, 1996).

As for studies conducted on older populations, who are more at risk for developing AD, there has also been some promise. With regard to age-related cognitive impairment and neurodegenerative disease, a study of hospitalized older medical patients found that those who received an exercise intervention training program demonstrated improved dual-task, verbal and arithmetic gait velocity test scores compared to those that received a standard hospital care control treatment (Saez de Asteasu et al., 2019). This indicates an improvement in cognitive function of older individuals who underwent exercise, leading to the question of whether such exercise could also improve cognitive function in those with AD.

Potential Effect of Exercise Intervention Modification on Cognition

As there is no consensus on the best strategy for exercise intervention, researchers at the Jilin Provincial Key Laboratory on Molecular and Chemical Genetics used cognitive exercise sessions, such as word games and puzzles, in conjunction with physical exercises, to assess their impact on overall cognition (Cui, Meng & Lin, et al., 2018). It was found that there were positive neuropsychological effects and improved executive functions for participants when both physical and cognitive exercise was performed, but it was also noted that simultaneously undergoing both had no significant difference to the outcome measures than performing both individually and separately. Overall, this study suggested that the amount and intensity of exercise are far more important than the type of exercise being done.

Gender as an Likely Moderator in AD, Exercise, and Cognition

Women are disproportionately affected by AD in comparison to men ("Women and Alzheimer's"). In fact, according to the Alzheimer's Associations, ⅔ of Americans living with AD are women. Therefore, the gender differences in the progression of AD, as well as the differences in response to interventions, are an important area of study in AD. There are also notable differences between healthy men and women with regards to their change in cognitive function after undergoing an exercise intervention, as well as differences in general cognitive decline during normal aging. The following is a review of some of the literature investigating the role of gender on the variables in question.

Gender Differences in Cognition in Response to Exercise Interventions

In a study conducted with 52 non-AD participants, the results showed that both male and female participants were relatively similar in IQ in the control and exercise group (Coleman, 2018). The participants completed an IQ assessment, along with activities such as walking and jump rope, as well as tests on selective attention and memory. In terms of accuracy in the selective attention task, females demonstrated a higher rate of attention than males did. Males responded faster than females during the encoding phase for the memory task, but females who responded slower had a higher recognition and object location memory test score. Overall, this particular study illustrates that men and women respond differently to exercise.

Gender Differences in Cognitive Impairment Symptoms in AD

There may be some biological basis for the observed gender differences in AD. One study examined the effect of sex on cognitive progression in subjects with high likelihood of mild cognitive impairment (MCI) due to AD. The changes in cognitive progression were followed in the study for up to 10 years through data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Sohn, D. et al, 2018). Measurements of cerebrospinal fluid, total-tau, and amyloid-beta (Aβ42) ratio values were used to classify AD patients with high or low likelihood of MCI due to AD. It was found that the mean worsening from baseline was greater in female subjects than in males. The study also found that an important allele linked to Alzheimer's, APOE ε4, has an effect on both the slope and curvature of AD cognitive assessment (ADAS-Cog11) decline. Heterozygotes and homozygotes in this allele declined in cognitive progression faster than non-carriers, and MCI female carriers of the APOE ε4 allele declined in cognitive progression faster than male carriers.

Gender Differences in Cognitive Decline during Natural Aging

A relevant study in this domain researched cognition and emotion in healthy men and women as they aged. The researchers tested 124 men and 117 premenopausal women and observed sex differences in verbal memory, spatial tasks, and motor tasks. The results showed no significant correlations between age and any of the behavioral measures in women (Gur & Gur, 2002). However, for men, increased age was associated with decrease in attention performance.

Other neuroanatomic studies done with MRI revealed three main gender differences. First, men are more affected by the progressive decrease in brain volume over time compared to women; second, women show less age related decline in cognitive function than men; third, age related cognitive decline begins earlier in men than in women (Gur & Gur, 2002).

The Present Study

The study discussed in this paper assesses different modes of exercise (stretching and toning versus aerobic exercise) and monitors whether they had a varying impact in early AD memory performance. For the first part of the present study, a replication of the Memory Composite analysis was conducted. This variable was of particular interest because memory decline that is greater than natural decline associated with aging is one of the distinguishing symptoms in AD. Memory is also affected by different kinds of exercise, as mentioned earlier, so the effect on memory as a result of the interaction between different exercise interventions over time is an important factor in the present study. Therefore, the extent of the effect of exercise intervention must be measured by taking the effect of time into account as well. The overall hypothesis tested in the replication analysis is whether the type of exercise (stretching and toning versus aerobic exercise) influences the normal, expected interaction between time and memory loss in individuals likely to develop AD.

The second part of the present study extended on the Memory Composite finding while adding an additional interaction variable -- sex. As discussed earlier, gender is also an important moderator in the interaction between several components of the replication study. There are gender differences in exercise intervention, cognitive responses, cognitive decline during aging, and symptoms of AD. Thus, the present study investigates the role of gender in the interaction between the type of exercise intervention and Memory Composite score over time. There is no clear consensus in the literature on whether a certain type of exercise plays a larger role in the different genders, but there have been significant findings on gender differences in cognitive decline over time. Consequently, the present study focuses on the interaction between gender and time in the Memory Composite score across both Treatment Arms. Additionally, a separate interaction model between gender and Treatment Arm across time is also included for the purpose of further investigation, as well as a three-way interaction model between all three aforementioned variables -- Sex, Timepoint, and Treatment Arm.

The present study hypothesizes that there would be a significant difference ($p < 0.05$) for all three interaction models, indicating that there is an interaction at play between the variables tested.

Methods

Participants

Participants (N = 68) in the original randomized pilot study were recruited by the researchers through a convenience sample of volunteers who passed telephone and in-person inclusion criteria and screening for probable AD based on standard clinical and cognitive tests. All participants were over 55 (M = 72.9, SD = 7.7) and in the early stages of AD. Inclusion criteria included mild cognitive impairment (MCI) based on standard clinical and cognitive test results and Clinical Dementia Rating. There were also several exclusion criteria, such as clinically-evident stroke, cancer in the last 5 years, and drug or alcohol abuse in the last 2 years.

Procedure

To ensure that the treatment groups were separated by similar characteristics, the groups were block randomized and stratified by age and sex by the researchers in the original study. There were 76 participants, with 68 participants completing the cognitive test battery study. The aerobic exercise, or AEx group, consisting of 34 participants completing the study, started with one hour of exercise and the amount of exercise time increased by 21 minutes each additional week until the goal of exercising for 2 ½ hours per week was fulfilled. These exercise sessions were carefully monitored and the participants did not engage in any other exercise aside from the time allotted in the study. The non-aerobic exercise group, or the ST (stretching and toning) group, which also consisted of 34 participants completing the study, did non-aerobic exercise such as stretching and toning and kept their heart rate under 100 bpm. Like the AEx group, the ST group was supervised by trainers for every session at the beginning of the study and then supervised for one session weekly. Each participant, trainer, and study coordinator met to review the intervention before the study began to ensure that each exercise session was monitored adequately, as mentioned in the original paper.

Outcome Measures

The outcome measures that the original study investigated were the memory composite score as the main outcome measure, as well as an assessment of functional ability and depressive symptoms as secondary outcome measures. All scores were taken at three timepoints - baseline, week 13, and week 26. The replication and extension portion of the present study focuses entirely on the memory composite score, which was calculated by standardizing the raw scores for the Logical Memory for both immediate and delayed recall, and Free and Cued Selective Reminding Test, which is also the sum of free recall. The Logical Memory test, a part of Wechsler memory scales, is commonly used to test individuals who have memory deficits or are diagnosed with disorders, including AD and dementia. Here, it was used in order to test the participants' performance on memory retention (Wechsler Memory Scale). The test is composed of two parts: in one part, participants are asked to recall a story immediately, whereas in the other part, there is a 20 minute delay before recalling a story (Gavett et al., 2016). In the original study, these values were compared to the mean and standard deviation of another study performed on healthy patients and standardized using these "normal" means and standard deviations. (Feldman et al., 2001) The memory composite was then calculated by taking the mean of these standardized values for logical memory, delayed memory and free recall for each individual.

Data Analysis

For all interaction model analysis, the lmerTest and lmTest packages were used in R. The emmeans package was used for the secondary analyses on the Memory Composite averages across time.

Replication Data Analysis

All analysis was conducted using R Studio. Analysis of the primary outcome measures was carried out by taking an average of the Logical Memory, Delayed Memory, and Free Recall standardized scores for each individual to find the Memory Composite score. The Memory Composite scores were then subset into two groups, Aerobic Exercise and Stretching and Toning. These groups were then subset further by Timepoint into three subgroups-- Baseline, Week 13, and Week 26. For each of the timepoints, the Memory Composite mean and standard deviations within each group was calculated (Figure 1, 2).

After calculating the Memory Composite Scores, multilevel modeling and a chi-square test were used to assess model fit for the interaction model. To execute this final component of the replication analysis, a main effects model was created between the Timepoint and Treatment Arm. A separate interaction model between Timepoint and Treatment Arm was also created to test the influence of time on performance in each of the two groups, controlling for Education and Baseline performance (using random intercepts). Finally, the main effects and interaction model were compared using a chi-square test to see if there was a significant difference between the two groups (Figure 3).

Extension Data Analysis

To extend the analysis using the data from the original study, the interaction between Sex and Treatment Arm, as well as Sex and Timepoint, was also tested. Thus, similar to the replication, a main effects model was created between Sex and one of the other two variables (Treatment Arm or Timepoint) and compared using chi-square analysis to an interaction model between the two variables in question, controlling for Education and Baseline performance (using random intercepts) (Figure 4, 8). The same method was employed to test the interaction between all three variables-- Sex, Treatment Arm, and Timepoint (Figure 10, 11).

Additional analysis was also conducted on the Sex by Timepoint interaction (Figure 4, 5). Sex by Timepoint is the main interaction model assessed in this study, since, as explained earlier, gender differences in cognitive decline seem to emerge more as a product of time, rather than exercise type. Thus, this data was visualized further by graphing the differences in averages of Memory Composite between the sexes across time (Figure 6).

Lastly, the Memory Composite Means in each arms for the two sexes were also graphed in order to visualize the interaction between Sex and Treatment Arm (Figure 9).

Results

The replication of the standard deviations and means for each Timepoint in both Treatment Arms yielded the same values as the original study (Figure 1, 2). There were no notable trends in this data.

In the replication of the chi-square analysis of the Timepoint by Treatment Arm interaction (Figure 3), similar values were found given the raw data used in the original study. The slight difference in chi square value (0.82 in the original study versus 0.87 in the present study) and p- value (0.66 and 0.65, respectively), were due to the different R packages (lme4 in the original study versus lmerTest and lmTest in the present study) used, but they both yield a similarly insignifiant p-value.

In the extension, the p-values found for the Sex by Timepoint Interaction (Figure 4) and Sex by Arm Interaction (Figure 8) were also insignificant (>0.05), indicating that gender may not play a role in the effect of time or exercise intervention on memory. The p-values at each point in the interaction model were found; these values were all insignificant, with the exception of the males at week 26, which had a p-value trending toward significance ($p = 0.082$) (Figure 5).

To visualize overall change of Memory Composite score through time, a graph of the means of the memory composite across treatment arms at each timepoint for both men and women was generated (Figure 6). In this graph, there is an evident increase in Memory Composite over time for men (-2.66 to -2.46), and a decrease for women (-2.57 to -2.64).

To look into this finding further, an analysis of the contrasts at each time interval was conducted (Figure 7), specifically to see if there are any significant differences between the means of the memory composites across different time intervals (Baseline to Week 13, Baseline to Week 26, and Week 13 to Week 26) in the two sexes. This analysis revealed insignificant p-values all greater than 0.05. However, one notable finding was the male p-value at the baseline to week 26 interval, which was trending toward significance ($p = 0.0837$).

As for the interaction between Sex and Treatment Arm, a graph of the Memory Composite Means in each Treatment Arm (Figure 9) reveals that there is a visible decrease in

Memory Composite Means (less negative) in males in the Aerobic Exercise group when compared to the Stretching and Toning male group, whereas female means did not vary as much between the two groups.

A three-way interaction model was also created between all three variables in question: Sex, Timepoint, and Arm (Figure 10, 11). The analysis of this model yielded an insignificant p-value (0.6954), indicating that there is no significant interaction between all three variables.

Discussion

In the replication of the original study, similar insignificant results for the chi-squared analysis of the Timepoint by Treatment Arm interaction were found, providing insufficient evidence to indicate that the type of exercise (Aerobic Exercise versus Stretching and Toning) influences the natural progression of memory loss in AD patients over time. Thus, our study cannot support our original hypothesis.

In the analyses extending on the original study, the p-values found for the Sex by Timepoint interaction and Sex by Treatment Arm interaction (Figure 4,8) were insignificant (> 0.05) possibly due to the small sample size ($N = 68$). However, the results show that the p-value for males at the baseline to week 26 interval is trending toward significant ($p = 0.082$), and serves as the sole data point supporting a Sex by Timepoint interaction and Sex by Treament Arm interaction (Figure 7). Also, the graph of the average Memory Composites over time (Figure 6) indicates that males experienced an increase in the Memory Composite scores over time whereas females experienced a decrease. Since this finding is from a small sample size, perhaps this data could be verified with larger groups. Although the analysis of the significance of Memory Composite change in different time intervals within the 26 weeks revealed p-values greater than 0.05 (Figure 7), indicating the statistically insignificant change in Memory

Composite over time, the figure shows a notable finding that the male p-value at the baseline to week 26 interval was trending toward significant ($p = 0.0837$). Overall, the extension analyses conducted in the present study yielded insignificant p-values, so our hypothesis that there is any interaction between Sex, Timepoint, and Treatment Arm cannot be supported, nor can the claims made in past literature about gender differences in these domains.

Related literature described earlier had suggested that there exists a difference between gender in relation to cognitive function, even though the present study found no such differences. However, in said studies, attention, verbal memory, spatial abilities, verbal memory, spatial tasks, and motor tasks were the primary outcome measures, whereas, in the present study, the memory composite score (an average of logical memory, delayed memory and free recall) was the outcome measure of interest. This difference in outcome measure is a possible explanation for the difference in conclusions between this study and those conducted elsewhere. In addition to this, something to note is that while the p-values may have not been significant, the values for males at week 26 in comparison to baseline was trending towards significance, which suggests that there is a possibility of relation (Figure 7). While the data currently contrasts that of the literature review, there is a possibility for similar outcomes if the extension was furthered in size or scope.

This study had limitations in its sample size, which reduces the statistical power of the extension interactions models. Thus, the results should be considered preliminary and further study is necessary to elucidate the true effect of gender in AD exercise intervention. Although through the extension, it was found that gender may not affect whether time or exercise intervention plays a role in memory, a relatively small sample size of N=68 was used, which could decrease the reliability of the findings. With a larger sample size, the true result may be more clear and the p-value may reach significance.

The replication of the pilot study was extended by investigating the effect of gender on exercise intervention over time. Although this extension did not lead to significant results, it provided a different perspective on looking at how other variables could affect the success of exercise intervention on subjects with AD in increasing memory composite. Thus, further areas for study could include exploring the potential influences of variables such as race, education level, and socio-economic background.

If tested on a larger population with more diverse demographics, the results could have several practical implications in the field of geriatrics, possibly helping better understand why AD is more prevelant among women, and perhaps how exercise treatment could be tailored to fit the specific sex and other demographics of the patient populaton.

Conclusion

The original study investigated the role of exercise interventions in ameliorating some of the symptoms of AD, among which Memory Composite was chosen as the primary focus of this paper. The present study replicated these findings on Memory Composite, indicating a lack of support for any significant role that exercise type plays in improving the generally worsening memory characteristic of AD over time. Because previous research has shown gender differences in prevalence and symptoms of AD, cognitive decline during aging, and response in cognitive tasks after exercise interventions, this study then extended this analysis to include a novel variable-- sex. To test the hypothesis that individuals with AD will present with gender differences in Memory Composite score after exercise interventions, three additional interaction models were assessed. The subsequent analyses disproved the original hypothesis, leading to the conclusion that gender may not play a significant role. However, further research must be conducted on a larger scale with more demographics taken into consideration. This would inform the ultimate goal of personalized exercise interventions for AD in the future, as the data shows what can be the most effective regimen to help alleviate cognitive decline. These findings, along with subsequent research, work towards the goal of finding constructive methods of intervention for those with AD.

References

"10 Early Signs and Symptoms of Alzheimer's." Alzheimer's Disease and Dementia, www.alz.org/alzheimers-dementia/10_signs.

Alzheimer's Association. (2019). 2019 Alzheimer's Disease Facts and Figures. Retrieved from https://www.alz.org/media/documents/alzheimers-facts-and-figures-2019-r.pdf

Asteasu, M. L. S. D., Martínez-Velilla, N., Zambom-Ferraresi, F., Casas-Herrero, Á., Cadore, E. L., Galbete, A., & Izquierdo, M. (2019). Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. PLOS Medicine, 16(7). doi: 10.1371/journal.pmed.1002852

Bature, F., Guinn, B.-A., Pang, D., & Pappas, Y. (2017). Signs and symptoms preceding the diagnosis of Alzheimer's disease: a systematic scoping review of literature from 1937 to 2016. BMJ Open, 7(8). doi: 10.1136/bmjopen-2016-015746

Christiansen, Sherry. (2018). What to Expect in the Late Stages of Alzheimer's Disease. Alzheimer's.net, www.alzheimers.net/what-to-expect-in-the-late-stages-of-alzheimers-disease/

Coleman, Matt, et al."Exercise Similarly Facilitates Men and Women's Selective Attention Task Response Times but Differentially Affects Memory Task Performance." *Frontiers in Psychology,* vol. 9, 2018, pp 1405, doi 10.3389/fpsyg.2018.01405.

Cui, M. Y., Lin, Y., Sheng, J. Y., Zhang, X., & Cui, R. J. (2012). Exercise Intervention Associated with Cognitive Improvement in Alzheimer's Disease. Neural Plasticity . doi: 10.1155/2018/9234105

Ellis, T., & Rochester, L. (2018). Mobilizing Parkinson's Disease: The Future of

Exercise. Journal of Parkinson's Disease, 8(s1). doi: 10.3233/jpd-181489

Feldman H, Sauter A, Donald A, Gelinas I, Gauthier S, Torfs K, et al. The disability assessment for dementia scale: a 12-month study of functional ability in mild to moderate severity Alzheimer disease. Alzheimer Dis Assoc Disord. 2001 Apr-Jun;15(2):89–95. pmid:11391090

Gavett, B. E., Gurnani, A. S., Saurman, J. L., Chapman, K. R., Steinberg, E. G., Martin, B., Chaisson, C. E., Mez, J., Tripodis, Y., & Stern, R. A. (2016). Practice Effects on Story Memory and List Learning Tests in the Neuropsychological Assessment of Older Adults. *PloS one*, *11*(10), e0164492. https://doi.org/10.1371/journal.pone.0164492

Gur, Raquel E. and Gur, Ruben E. (2002). Gender Differences in Aging: Cognition, Emotions, and Neuroimaging Studies. *PMC*, *4(2)*, pmid: 22033483

Herold, F., Törpel, A., Schega, L., & Müller, N. G. (2019). Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements – a systematic review. *European Review of Aging and Physical Activity, 16*(1). doi: 10.1186/s11556-019-0217-2

Hogervorst, E., Riedel, W., Jeukendrup, A., & Jolles, J. (1996). Cognitive Performance after Strenuous Physical Exercise. *Perceptual and Motor Skills, 83*(2), 479–488. doi: 10.2466/pms.1996.83.2.479

Morris, J.K., Vidoni, E.D., Johnson, D.K., Van Sciver, A., Mahnken, J.D., Honea, R.A., et al. (2017) Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PLoS ONE 12*(2):e0170547. doi:10.1371/journal.pone.0170547

Morris, J. & Vidoni, E. (2017) "Alzheimer's Disease Exercise Program Trial" Harvard Dataverse, V1 doi:10.7910/DVN/ER8ICT

N. Schuff, N. Woerner, L. Boreta, T. Kornfield, L. M. Shaw, J. Q. Trojanowski, … M. W. Weiner. (2009). MRI of Hippocampal Volume Loss in Early Alzheimer's Disease in Relation to ApoE Genotype and Biomarkers. *PMC*, *132(4)*, doi: 10.1093/brain/awp007

Robertson, Sally. "What Is Grey Matter?" News, 23 Aug. 2018, www.news-medical.net/health/What-is-Grey-Matter.aspx.

RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.

Sohn, D., Shpanskaya, K., Lucas, J.E., Petralla, J.R., Saykin, A.J., Tanzi, R.E., Samatova, N.F., & Doraiswamy, P.M. (2018). Sex Differences in Cognitive Decline in Subjects with High Likelihood of Mild Cognitive Impairment due to Alzheimer's disease. *Scientific Reports, 8*(7490), doi:10.1038/s41598-018-25377-w

Stephen, Elena, Kauffmann, Louise, Renard, Félix, … Monica. (2018, July 18). Gray Matter Volume and Cognitive Performance During Normal Aging. A Voxel-Based Morphometry Study. Retrieved from https://www.frontiersin.org/articles/10.3389/fnagi.2018.00235/full.

Thompson , P. M., Hayashi, K. M., Zubicaray, G. de, Janke , A. L., Rose , S. E., Semple, J., … Toga , A. W. (2003). Dynamics of Gray Matter Loss in Alzheimer's Disease. The Journal of Neuroscience , 23(3). doi: https://doi.org/10.1523/JNEUROSCI.23-03-00994.2003

Vidoni, E. D., Johnson, D. K., Morris, J. K., Sciver, A. V., Greer, C. S., Billinger, S. A., … Burns, J. M. (2015). Dose-Response of Aerobic Exercise on Cognition: A Community-Based, Pilot Randomized Controlled Trial. Plos One, 10(7). doi: 10.1371/journal.pone.0131647

Wang, Q., Hu, J., Liu, Y., Li, J., Liu, B., Li, M., & Lou, S. (2019). Aerobic Exercise Improves Synaptic-Related Proteins of Diabetic Rats by Inhibiting FOXO1/NF-κB/NLRP3 Inflammatory Signaling Pathway and Ameliorating PI3K/Akt Insulin Signaling Pathway. Journal of Molecular Neuroscience, 69(1), 28–38. doi: 10.1007/s12031-019-01302-2

Wechsler Memory Scale. (n.d.). Retrieved from https://www.sciencedirect.com/topics/neuroscience/wechsler-memory-scale

"Women and Alzheimer's." Alzheimer's Disease and Dementia, www.alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s.

Saez de Asteasu ML, Martınez-Velilla N, Zambom-Ferraresi F, Casas-Herrero A, Cadore EL, Galbete A, et al. (2019) Assessing the impact of physical exercise on cognitive function in older medical patients during acute hospitalization: Secondary analysis of a randomized trial. PLoS Med 16(7): e1002852. https://doi.org/10.1371/journal.pmed.1002852