

**Exercise From Afar: Progressing At-Risk Adults to Independent  
Exercise for Dementia Risk Reduction**

April 1, 2024

NCT #: TBD

## **SPECIFIC AIMS**

**Aim 1. Determine the impact of a technology-driven exercise program on exercise adherence, exercise efficacy and exercise enjoyment.** Providing a personalized exercise program via a smart phone application reduces the need for personal trainer or group exercise class. Providing memberships at local fitness facilities provides the opportunity for participants to choose to exercise at home or at a fitness facility. Together, these delivery characteristics may reduce barriers to exercise for Rural adults. We hypothesize that Rural adults will report high exercise adherence, efficacy and enjoyment following this program.

**Aim 2. Determine the impact of a technology-driven exercise program on biomarkers associated with dementia risk.** Exercise is associated with disease risk reduction. Cardiovascular exercise is known to reduce biomarkers associated with disease risk (LDL, cholesterol, blood glucose, etc.). We hypothesize that participants with high exercise adherence will see the greatest improvements in biomarkers associated with reduced dementia risk.

## **RESEARCH STRATEGY**

### **Significance**

Alzheimer's disease (AD) affects more than 6.1 million Americans and costs our national economy nearly \$400 billion per year (1). Advancing age is the single greatest risk factor. Alzheimer's is estimated to affect one in every eight Americans over 65, and more than half of those past the age of 85 either have AD or show signs of developing the disease. For Latino individuals, the risk of AD is even higher; twice that of Caucasian older adults. Alzheimer's disease has reached the status of being a public health crisis with a diagnosis every 66 seconds. Kansas has an estimated 53,000 residents over 65 diagnosed with AD. Research suggests if we can push back the onset of AD by 5 years, we could reduce the prevalence of AD in the state of Kansas by 50%.

Rural Americans (RA) report significantly higher percentages of obesity and chronic disease than their urban counterparts (4, 13). However, rural individuals face different barriers to physical activity and exercise than urban-dwelling individuals (3, 7). Six key lifestyle behaviors have been identified as AD risk reducing behaviors; physical activity and exercise, nutrition, social engagement, cognitive engagement, socialization, sleep and stress management (5). Research suggests that individuals who regularly participate in these behaviors are at a lower risk of developing cognitive impairment than those who do not (11, 16, 20, 25, 27, 30, 32, 45). Rural Americans report lower attainment of education, less daily physical activity (both by choice and due to chronic health conditions), higher all cause death rates and greater use of tobacco products among all ages (3, 4, 8, 10, 12, 14). Risk reduction education and programming is essential to address and preclude further health disparities in these underserved communities. Cultural differences may also play a significant role in both AD risk and perception of barriers and benefits (of healthy lifestyle practices) (3, 7, 9, 14).

Given that nearly 50% of all individuals are likely to experience some form of cognitive decline by age 85, it is imperative that preventative measures be integrated into communities. Rural Americans require such programs to be tailored to their specific needs and address their unique barriers.

### **Innovation**

Health disparity research exists and tells us that Rural Americans experience different and more numerous barriers to healthy lifestyle behaviors (specifically exercise) than do their urban-dwelling counterparts (2-4, 6-13). Exercise trials have investigated the impact of structured, supervised exercise on cognition and markers related to cognitive decline risk (26-31, 33-36, 44, 45, 51, 63, 72, 74, 79, 81, 83). Exercise seems to be effective at reducing risk for cognitive decline, as well as a myriad of other chronic diseases. However, most exercise trials are conducted within a very controlled setting, often lacking what would be deemed a 'real-world' feel to them. They also don't address financial and geographic constraints. Our goal is to provide a more 'real-world' exercise experience for Rural adults that lends itself to disease risk reduction and overall health improvement. The purpose of this study is to investigate the efficacy of a technology-driven independent exercise program on health outcomes associated with dementia risk in underactive rural adults. Our goal is to create a safe, effective means of

delivering personalized exercise programming to rural adults that reduces barriers to exercise, improves physical fitness and biomarkers associated with dementia risk and lends itself to exercise adherence in a population that is at an increased risk for cognitive decline.

### **Approach**

This is a randomized controlled exercise trial. Participants will be recruited from pre-determined rural locations across Kansas. Recruitment will be conducted via radio, newspaper, traditional recruitment flyers at specific locations and other methods as deemed necessary. Underactive adults (n=50), ages 40-70 years, from federally designated rural and frontier Kansas counties will be recruited to participate in this study. Middle aged adults will be included in the study as they are at an age when successful behavior change is more probable (than older, institutionalized adults); older adults will be included as they are in the high-risk category for dementia. The inclusionary and exclusionary criteria for participation is detailed in Table 1.

<b>Table 1. Inclusion and Exclusion Criteria</b>	
<u>Inclusion criteria</u>	<ul style="list-style-type: none"><li>- Age 40 to 70 years</li><li>- Characterized as underactive by the TAPA.</li><li>- Able to read and converse in English</li><li>- Willing and able to install an application on their smart phone (with assistance)</li></ul>
<u>Exclusion criteria</u>	<ul style="list-style-type: none"><li>-Myocardial infarction or symptoms of coronary artery disease in the last 2yrs</li><li>-Uncontrolled hypertension within the last 6 months</li><li>-Cancer in the last 2yrs (except non-metastatic basal or squamous cell carcinoma)</li><li>-Significant pain or musculoskeletal disorder that would prohibit participation in an exercise program</li><li>-Possible/probably dementia or mild cognitive impairment (MCI) base on adjudication</li><li>-Physician concern regarding safety or completion of the study</li></ul>

Potential participants will be screened using the TAPA (1). Following screening, participants will complete baseline physical fitness and health assessments, supervised by the research team. This will require travel by the research team to various rural Kansas locations. The assessments will be those considered reliable, validated 'field tests' and can be easily administered with minimal exercise equipment. Blood glucose and cholesterol levels will be measured as well, using a device commonly used in the field (total, LDL, HDL and triglycerides). Additional baseline assessments may include, but are not limited to: cognitive assessments, quality of life (QOL), perceived stress, and perceived stress. Following completion of baseline assessments, participants will be randomized to one of two groups:

- 1) Exercise (EX); This group will be given structured exercise programming for 16 weeks.
- 2) Control (CON); This group will serve as the underactive control for this study. At the end of 16 weeks, they will be offered the same 16-week structured exercise program as the exercise group.

A personal training/fitness app will be installed on each participant's smart phone or tablet. The application used will be a highly-rated, commonly used fitness app and will be used in this study to design and deliver exercise programming and track exercise participation, adherence and progression over the course of the study. The study team will record exercise instruction videos that can be accessed by all participants at any time throughout the study. The particular app used will allow the research team to organize exercise videos into structured training sessions, allowing participants to exercise on their own, at the location of their choice, with ample instruction. The app will also allow participants to record themselves performing various exercises and send them to the research team for analysis of technique and safety. Communication between study personnel and participants will be delivered via the app. Phone calls and/or Zoom sessions will be offered as an alternative if necessary. During the initial project period (16 weeks), only the EX group will be given access to the structured exercise plan.

### **Exercise Intervention**

The exercise intervention will consist of 3-5 exercise evidence-based exercise sessions weekly for a total of 16 weeks. The target goal for all participants will be 75-150 minutes of aerobic exercise and 2-3 strength training sessions weekly. Exercise will be progressive in nature and participants will be

encouraged to achieve the target goal for exercise by week 8 of the study and maintain the target goal for weeks 8-16. All prescribed exercise will follow national governing body recommendations and include specific exercises found in previous work to be beneficial for physical health and brain plasticity. Following the exercise intervention, all baseline assessments will be repeated. Data will be compared to determine the impact of the exercise program on each variable (i.e. dementia risk biomarkers, QOL, physical fitness, etc.).

### **Data Analysis**

Data collected from this study will be analyzed using statistical analysis software (SPSS) to determine differences, if any, between groups for each measure. We plan to collaborate with a qualitative statistician who will assist with the qualitative statistical analyses.

### **Outcomes**

Findings from this study will be presented at a state or regional conference, in addition to the K-INBRE Annual Symposium. The undergraduate research assistants and faculty mentor will work collaboratively to submit at least one manuscript for publication. Data from this study will be considered pilot data and used to apply for an R15/R16 award to further investigate effective means of exercise delivery for underserved and at-risk populations across Kansas and beyond.

### **Alternative Strategies**

There is the possibility that some older adults will not have access to a smart phone or feel comfortable using the fitness app on their phone or tablet. In this case, printed materials and exercise logs will be provided to these participants. All videos recorded will also be kept on a Google drive and the link to that drive will be offered to those participants. While data from these participants would not be relevant to the efficacy of technology-driven exercise delivery, it would be relevant to unsupervised exercise from afar. This would still provide valuable information about exercise adherence, motivation and associated physiological adaptations.

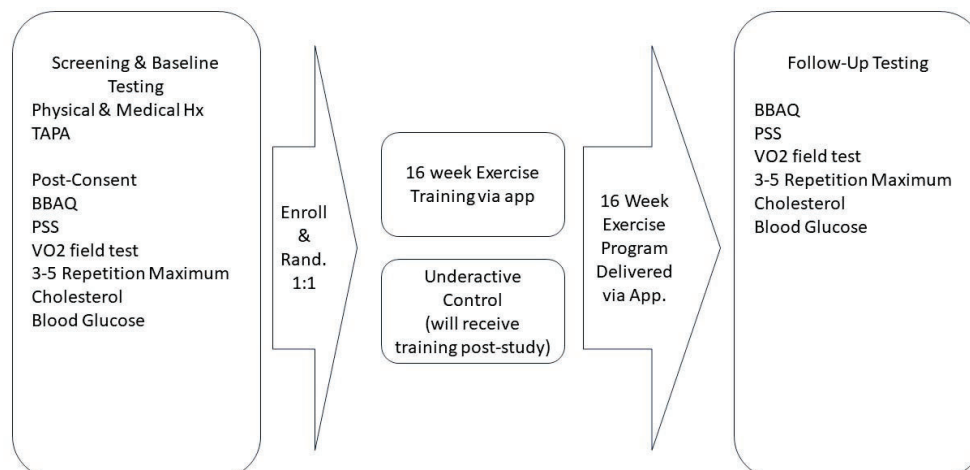
### **Timeline**

A detailed study timeline is presented in Figure 1.

## **STUDENT MENTORING**

The undergraduate research assistants (UGRAs) and PI (faculty mentor) will meet weekly throughout the course of the entirety of this project (SU24-SP25). In addition, the PI will supervise all program design, exercise video creation and dissemination. The UGRAs will be allowed more independence as their skills and confidence increase throughout the study period. As the students become increasingly competent using the fitness app and communicating with participants, they will gain greater responsibility and independence. Exercise program design and progression will continue to be overseen by the PI, with ample input from the UGRAs. This project will be a truly collaborative effort and provide great professional development and skill development opportunities for the UGRAs. UGRAs will be responsible for assisting in the data analysis and manuscript writing following completion of the study.

**Figure 1. Study timeline.**



## References

1. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021 Mar;17(3):327-406. doi: 10.1002/alz.12328. Epub 2021 Mar 23. PMID: 33756057.
2. Erwin PC, Fitzhugh EC, Brown KC, et al. Health disparities in rural areas: the interaction of race, socioeconomic status, and geography. *J Health Care Poor Underserved*. 2010;21(3):931-945.
3. Wilcox S, Castro C, King AC, Housemann R and Brownson RC. Determinants of leisure time physical activity in rural compared with urban older and ethnically diverse women in the United States. *J Epidemiol Community Health*. 200; (54): 667-672.
4. Befort CA, Niaman N and Perri MG. Prevalence of obesity among adults from rural and urban areas of the United States: findings from NHANES (2005-2008). *Journal of Rural Health*. 2012; 28(4): 392-397
5. Burns JM, Vidoni ED. KU ADC Smart Aging Curriculum. 2015.
6. Braveman B. AOTA's statement on health disparities. *Am J Occup Ther*. 2006;60(6):679.
7. Aronson RE, Oman RF. Views on exercise and physical activity among rural-dwelling senior citizens. *Journal of Rural Health*. 2004; 20(1): 76-79.
8. Meit M, Knudson A, Gilbert T, Yu AT-C, Tannenbaum E, Ormson E, TenBroeck S, Bayne A, Popat S. The 2014 Update of the Rural-Urban Chartbook. NORC Walsh Center for Rural Health Analysis: Rural Health Research & Policy Centers. 2014.
9. Murimi MW, Harpel T. Practicing preventative health: the underlying culture among low-income rural populations. *Journal of Rural Health*. 2010; 26(2010):273-282.
10. Althoff T, Sosic R, Hicks JL, King AC, Delp AL, Leskovec J. Large-scale physical activity data reveal worldwide activity inequality. *Nature*. 2017; 547:336-351.
11. Nagamatsu LS, Flicker L, Kramer AF, Voss MW, Erickson KI, Hsu CL, Liu-Ambrose T. Exercise is medicine, for the body and the brain. *Br J Sports Med*. 2014; 48(12):943-944.
12. Bolin JN, Bellamy GR, Ferdinand AO, Vuong AM, Kash BA, Schulze A, Hedluser JW. Rural Healthy People 2020: new decade, same challenges. 2015; Summer;31(3):326-333.
13. Trivedi T, Liu J, Probst J, Merchant A, Jhones S, Martin AB. Obesity and obesity-related behaviors among rural and urban adults in the USA. *Rural and Remote Health*. 2015;Oct-Dec;15(4):3267.
14. Mayer, C. J., Steinman, L., Williams, B., Topolski, T. D., & LoGerfo, J. (2008). Telephone Assessment of Physical Activity (TAPA) [Database record]. APA PsycTests. <https://doi.org/10.1037/t01539-000>
15. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A. Ageing, fitness and neurocognitive function. *Nature*. 1999;400(6743):418-9. PubMed PMID: 10440369.
16. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108(7):3017-22. Epub 2011/02/02. doi: 10.15950108 [pii]
17. 10.1073/pnas.1015950108. PubMed PMID: 21282661; PMCID: 3041121.
18. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women: Women Who Walk. *Archives of Internal Medicine*. 2001;161(14):1703-8. PubMed PMID: 4174.

19. Pignatti F, Rozzini R, Trabucchi M, Yaffe K. Physical Activity and Cognitive Decline in Elderly Persons. *Archives of Internal Medicine*. 2002;162(3):361-2. PubMed PMID: 4126.
20. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Archives of Neurology*. 2001;58(3):498-504. PubMed PMID: 3282.
21. Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat HW, Shigeoka JW, Wood JS, Bradford DC. Aerobic Exercise Training and Improved Neuropsychological Function of Older Individuals. *Neurobiology of Aging*. 1984;5(1):35-42. PubMed PMID: 4169.
22. Weuve J, Kang JH, Manson JE, Breteler MMB, Ware JH, Grodstein F. Physical Activity, Including Walking, and Cognitive Function in Older Women. *JAMA: The Journal of the American Medical Association*. 2004;292(12):1454-61. PubMed PMID: 4192.
23. Hindin SB, Zelinski EM. Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. *J Am Geriatr Soc*. 2012;60(1):136-41. doi: 10.1111/j.1532-5415.2011.03761.x. PubMed PMID: 22150209.
24. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science*. 2003;14(2):125-30. PubMed PMID: 3788.
25. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, White SM, Wojcicki TR, McAuley E, Kramer AF. Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*. 2009;19(10):1030-9. Epub 2009/01/06. doi: 10.1002/hipo.20547. PubMed PMID: 19123237.
26. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *British Journal of Sports Medicine*. 2018;52(3):154. doi: 10.1136/bjsports-2016-096587.
27. Brasure M, Desai P, Davila H, Nelson VA, Calvert C, Jutkowitz E, Butler M, Fink HA, Ratner E, Hemmy LS, McCarten JR, Barclay TR, Kane RL. Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review. *Annals of Internal Medicine*. 2018;168(1):30-8. doi: 10.7326/M17-1528.
28. Best JR, Chiu BK, Liang Hsu C, Nagamatsu LS, Liu-Ambrose T. Long-Term Effects of Resistance Exercise Training on Cognition and Brain Volume in Older Women: Results from a Randomized Controlled Trial. *Journal of the International Neuropsychological Society*. 2015;21(10):745-56. Epub 2015/11/19. doi: 10.1017/S1355617715000673.
29. Kramer AF, Colcombe S. Fitness Effects on the Cognitive Function of Older Adults: A Meta-Analytic Study—Revisited. *Perspectives on Psychological Science*. 2018;13(2):213-7. doi: 10.1177/1745691617707316.
30. Herold F, Törpel A, Schega L, Müller NG. 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*. 2019;16(1):10. doi: 10.1186/s11556-019-0217-2.
31. Li Z, Peng X, Xiang W, Han J, Li K. The effect of resistance training on cognitive function in the older adults: a systematic review of randomized clinical trials. *Aging clinical and experimental research*. 2018;30(11):1259-73. Epub 2018/07/15. doi: 10.1007/s40520-018-0998-6. PubMed PMID: 30006762.
32. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES, Jr., Cox NJ, Dunbar-Jacob JM, Granieri EC, Hunt G, McGarry K, Patel D, Potosky AL, Sanders-Bush E, Silberberg D, Trevisan M. National Institutes of Health State-of-the-Science Conference statement: preventing alzheimer disease and cognitive decline. *Ann Intern Med*. 2010;153(3):176-81. Epub 2010/06/16. doi: 0003-4819-153-3-201008030-00260 [pii] 10.1059/0003-4819-153-3-201008030-00260. PubMed PMID: 20547888.



33. Snowden M, Steinman L, Mochan K, Grodstein F, Prohaska TR, Thurman DJ, Brown DR, Laditka JN, Soares J, Zweiback DJ, Little D, Anderson LA. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. *J Am Geriatr Soc.* 2011;59(4):704-16. doi: 10.1111/j.1532-5415.2011.03323.x. PubMed PMID: 21438861.
34. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, Skinner JS. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc.* 2009;41(7):1510-30. Epub 2009/06/12. doi: 10.1249/MSS.0b013e3181a0c95c. PubMed PMID: 19516148.
35. Healthy People 2020. [Internet]. Office of Disease Prevention and Health Promotion. 2013 [cited Sept. 3, 2013]. Available from: <http://healthypeople.gov/2020/topicsobjectives2020/nationaldata.aspx?topicId=33>.
36. Erickson KI, Grove GA, Burns JM, Hillman CH, Kramer AF, McAuley E, Vidoni ED, Becker JT, Butters MA, Gray K, Huang H, Jakicic JM, Kamboh MI, Kang C, Klunk WE, Lee P, Marsland AL, Mettenburg J, Rogers RJ, Stillman CM, Sutton BP, Szabo-Reed A, Verstynen TD, Watt JC, Weinstein AM, Wollam ME. Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE): Protocol. *Contemporary Clinical Trials.* 2019;85:105832. doi: <https://doi.org/10.1016/j.cct.2019.105832>.
37. Schutzer KA, Graves BS. Barriers and motivations to exercise in older adults. *Prev Med.* 2004;39(5):1056-61. doi: 10.1016/j.ypmed.2004.04.003. PubMed PMID: 15475041.
38. Cassilhas RC, Lee KS, Fernandes J, Oliveira MG, Tufik S, Meeusen R, de Mello MT. Spatial memory is improved by aerobic and resistance exercise through divergent molecular mechanisms. *Neuroscience.* 2012;202:309-17. Epub 2011/12/14. doi: 10.1016/j.neuroscience.2011.11.029. PubMed PMID: 22155655.
39. Liu-Ambrose T, Donaldson MG. Exercise and cognition in older adults: is there a role for resistance training programmes? *British journal of sports medicine.* 2009;43(1):25-7. Epub 2008/11/21. doi: bjsm.2008.055616 [pii] 10.1136/bjsm.2008.055616. PubMed PMID: 19019904.
40. Hayes SM, Hayes JP, Cadden M, Verfaellie M. A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. *Frontiers in aging neuroscience.* 2013;5:31. doi: 10.3389/fnagi.2013.00031. PubMed PMID: 23874299; PMCID: 3709413.
41. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011;86(9):876-84. Epub 2011/09/01. doi: 10.4065/mcp.2011.0252. PubMed PMID: 21878600; PMCID: PMC3258000.
42. Colcombe SJ, Kramer AF, McAuley E, Erickson KI, Scalf P. Neurocognitive aging and cardiovascular fitness: recent findings and future directions. *J Mol Neurosci.* 2004;24(1):9-14. Epub 2004/08/18. doi: JMN:24:1:009 [pii]. PubMed PMID: 15314244.
43. National Institute on Aging. Growing Older in America: the Health and Retirement Study. Bethesda, MD: National Institutes of Health, 2007.
44. Cammisuli D, Innocenti A, Franzoni F, Pruneti C. Aerobic exercise effects upon cognition in Mild Cognitive Impairment: A systematic review of randomized controlled trials. *Archives italiennes de biologie.* 2017;155(1/2):55-63.
45. Mortimer JA, Stern Y. Physical exercise and activity may be important in reducing dementia risk at any age. *Neurology.* 2019;92(8):362-3. doi: 10.1212/wnl.0000000000006935.
46. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *American journal of public health.* 1998;88:1337-42. PubMed PMID: 3190.

47. Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory Fitness and the Risk for Stroke in Men. *Archives of Internal Medicine*. 2003;163(14):1682-8. PubMed PMID: 4010.
48. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical Fitness as a Predictor of Mortality among Healthy, Middle-Aged Norwegian Men. *The New England Journal of Medicine*. 1993;328(8):533-7. PubMed PMID: 4012.
49. Laukkanen JA, Lakka TA, Rauramaa R, Kuhanen R, Venäläinen JM, Salonen R, Salonen JT. Cardiovascular Fitness as a Predictor of Mortality in Men. *Archives of Internal Medicine*. 2001;161(6):825-31. doi: 10.1001/archinte.161.6.825.
50. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A*. 1990;87(14):5568-72. Epub 1990/07/01. PubMed PMID: 1695380; PMCID: 54366.
51. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci*. 2002;25(6):295-301. Epub 2002/06/28. doi: S0166223602021434 [pii]. PubMed PMID: 12086747.
52. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimer's Disease. *Journal of Neuroscience*. 2005;25(17):4217-21.
53. Nation DA, Hong S, Jak AJ, Delano-Wood L, Mills PJ, Bondi MW, Dimsdale JE. Stress, exercise, and Alzheimer's disease: a neurovascular pathway. *Med Hypotheses*. 76(6):847-54. Epub 2011/03/15. doi: S0306-9877(11)00085-5 [pii] 10.1016/j.mehy.2011.02.034. PubMed PMID: 21398043; PMCID: 3094492.
54. Radak Z, Hart N, Sarga L, Koltai E, Atalay M, Ohno H, Boldogh I. Exercise plays a preventive role against Alzheimer's disease. *J Alzheimers Dis*. 20(3):777-83. Epub 2010/02/26. doi: R070V32348243108 [pii] 10.3233/JAD-2010-091531. PubMed PMID: 20182027.
55. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, Morris JC, Head D. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*. 2010;68(3):311-8. Epub 2010/09/08. doi: 10.1002/ana.22096. PubMed PMID: 20818789; PMCID: 2936720.
56. Seals DR, Hagberg JM, Hurley BF, Ehsani AA, Holloszy JO. Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. *JAMA: The Journal of the American Medical Association*. 1984;252(5):645-9. PubMed PMID: 3835.
57. Kirwan JP, Kohrt WM, Wojta DM, Bourey RE, Holloszy JO. Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. *J Gerontol*. 1993;48(3):M84-M90. PubMed PMID: 3839.
58. Nichol K, Deeny SP, Seif J, Camaclang K, Cotman CW. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimers Dement*. 2009;5(4):287-94. Epub 2009/06/30. doi: S1552-5260(09)00060-0 [pii] 10.1016/j.jalz.2009.02.006. PubMed PMID: 19560099.
59. Garcia-Mesa Y, Lopez-Ramos JC, Gimenez-Llort L, Revilla S, Guerra R, Gruart A, Laferla FM, Cristofol R, Delgado-Garcia JM, Sanfeliu C. Physical exercise protects against Alzheimer's disease in 3xTg-AD mice. *J Alzheimers Dis*. 24(3):421-54. Epub 2011/02/08. doi: 847Q3J85285P1U07 [pii] 10.3233/JAD-2011-101635. PubMed PMID: 21297257.
60. Elsayy B, Higgins KE. Physical activity guidelines for older adults. *American family physician*. 2010;81(1):55-9. Epub 2010/01/08. PubMed PMID: 20052963.



61. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334-59. Epub 2011/06/23. doi: 10.1249/MSS.0b013e318213fefb. PubMed PMID: 21694556.
62. Albert MS, Jones K, Savage CR, Berkman L, Seeman T, Blazer D, Rowe JW. Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychol Aging.* 1995;10(4):578-89. PubMed PMID: 4175.
63. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. Exercise Is Associated with Reduced Risk for Incident Dementia among Persons 65 Years of Age and Older. *Ann Intern Med.* 2006;144(2):73-81.
64. Buchman AS, Boyle PA, Yu L, Shah RC, Wilson RS, Bennett DA. Total daily physical activity and the risk of AD and cognitive decline in older adults. *Neurology.* 2012;78(17):1323-9. Epub 2012/04/21. doi: 10.1212/WNL.0b013e3182535d35. PubMed PMID: 22517108.
65. Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, Kramer AF. Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(2):M176-M80. PubMed PMID: 3623.
66. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM, Swerdlow RH. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology.* 2008;71(3):210-6. Epub 2008/07/16. doi: 10.1212/01.wnl.0000317094.86209.cb. PubMed PMID: 18625967.
67. Honea RA, Thomas GP, Harsha A, Anderson HS, Donnelly JE, Brooks WM, Burns JM. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2009;23(3):188-97. Epub 2009/10/09. doi: 10.1097/WAD.0b013e31819cb8a200002093-200907000-00003 [pii]. PubMed PMID: 19812458.
68. Hassmen P, Koivula N. Mood, physical working capacity and cognitive performance in the elderly as related to physical activity. *Aging-Clinical and Experimental Research.* 1997;9(1-2):136-42. PubMed PMID: 4164.
69. Williams P, Lord SR. Effects of group exercise on cognitive functioning and mood in older women. *Australian and New Zealand Journal of Public Health.* 1997;21(1):45-52. PubMed PMID: 4163.
70. Hill RD, Storandt M, Malley M. The impact of long-term exercise training on psychological function in older adults. *J Gerontol.* 1993;48(1):12-7. PubMed PMID: 4170.
71. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S. Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences.* 2004;101(9):3316-21. PubMed PMID: 3622.
72. Borst SE. Interventions for sarcopenia and muscle weakness in older people. *Age Ageing.* 2004;33(6):548-55. Epub 2004/09/24. doi: 10.1093/ageing/afh201afh201 [pii]. PubMed PMID: 15385272.
73. Liu CJ, Latham NK. Progressive resistance strength training for improving physical function in older adults. *The Cochrane database of systematic reviews.* 2009(3):CD002759. doi: 10.1002/14651858.CD002759.pub2. PubMed PMID: 19588334.
74. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, Mello MT. The impact of resistance exercise on the cognitive function of the elderly. *Med Sci Sports Exerc.*

- 2007;39(8):1401-7. Epub 2007/09/01. doi: 10.1249/mss.0b013e318060111f00005768-200708000-00024 [pii]. PubMed PMID: 17762374.
75. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. *Arch Intern Med*. 2010;170(2):170-8. Epub 2010/01/27. doi: 10.1001/archinternmed.2009.494. PubMed PMID: 20101012.
76. Willis LH, Slentz CA, Bateman LA, Shields AT, Piner LW, Bales CW, Houmard JA, Kraus WE. Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. *J Appl Physiol* (1985). 2012;113(12):1831-7. doi: 10.1152/jappphysiol.01370.2011. PubMed PMID: 23019316; PMCID: 3544497.
77. Davidson LE, Hudson R, Kilpatrick K, Kuk JL, McMillan K, Janiszewski PM, Lee S, Lam M, Ross R. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. *Arch Intern Med*. 2009;169(2):122-31. Epub 2009/01/28. doi: 10.1001/archinternmed.2008.558. PubMed PMID: 19171808.
78. Sillanpaa E, Hakkinen A, Punnonen K, Hakkinen K, Laaksonen DE. Effects of strength and endurance training on metabolic risk factors in healthy 40-65-year-old men. *Scandinavian journal of medicine & science in sports*. 2009;19(6):885-95. doi: 10.1111/j.1600-0838.2008.00849.x. PubMed PMID: 19508653.
79. Vidoni ED, Johnson DK, Morris JK, Van Sciver A, Greer CS, Billinger SA, Donnelly JE, Burns JM. Dose-Response of Aerobic Exercise on Cognition: A Community-Based, Pilot Randomized Controlled Trial. *PLOS ONE*. 2015;10(7):e0131647. doi: 10.1371/journal.pone.0131647.
80. Billinger SA, Vidoni ED, Morris JK, Thyfault JP, Burns JM. Exercise test performance reveals evidence of the cardiorespiratory fitness hypothesis. *Journal of aging and physical activity*. 2017;25(2):240-6.
81. Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiology of aging*. 2011. Epub 2011/07/12. doi: S0197-4580(11)00193-X [pii]10.1016/j.neurobiolaging.2011.05.010. PubMed PMID: 21741129.
82. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39(8):1435-45. Epub 2007/09/01. doi: 10.1249/mss.0b013e3180616aa200005768-200708000-00028 [pii]. PubMed PMID: 17762378.
83. Sanders LMJ, Hortobagyi T, la Bastide-van Gemert S, van der Zee EA, van Heuvelen MJG. Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. *PLoS One*. 2019;14(1):e0210036. Epub 2019/01/11. doi: 10.1371/journal.pone.0210036. PubMed PMID: 30629631; PMCID: PMC6328108.
84. Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. *Prev Chronic Dis*. 2006;3(4):A118. Epub 2006/09/19. doi: A118 [pii]. PubMed PMID: 16978493; PMCID: 1779282.
85. Aging NIO. Exercise & Physical Activity: Your Everyday Guide from the National Institute on Aging at NIH. In: Services DoHaH, editor. 2009.
86. American College of Sports M, Riebe D, Ehrman JK, Liguori G, Magal M. ACSM's guidelines for exercise testing and prescription2018.

87. Ehrman JK, editor. ACSM's resource manual for guidelines for exercise testing and prescription. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010.
88. van Boxtel MP, Paas FG, Houx PJ, Adam JJ, Teeken JC, Jolles J. Aerobic capacity and cognitive performance in a cross-sectional aging study. *Med Sci Sports Exerc.* 1997;29(10):1357-65. PubMed PMID: 4162.
89. Johnson DK, Storandt M, Morris JC, Galvin JE. Longitudinal study of the transition from healthy aging to Alzheimer disease. *Archives of neurology.* 2009;66(10):1254-9. Epub 2009/10/14. doi: 66/10/1254 [pii]10.1001/archneurol.2009.158. PubMed PMID: 19822781.
90. Vidoni ED, Honea RA, Billinger SA, Swerdlow RH, Burns JM. Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years. *Neurobiol Aging.* 2012;33(8):1624-32. Epub 2011/05/03. doi: 10.1016/j.neurobiolaging.2011.03.016. PubMed PMID: 21531480; PMCID: 3156963.
91. Erickson KI, Raji CA, Lopez OL, Becker JT, Rosano C, Newman AB, Gach HM, Thompson PM, Ho AJ, Kuller LH. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. *Neurology.* 2010;75(16):1415-22. Epub 2010/10/15. doi: WNL.0b013e3181f88359 [pii]10.1212/WNL.0b013e3181f88359. PubMed PMID: 20944075.
92. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, Wilkins HM, Brooks WM, Billinger SA, Swerdlow RH, Burns JM. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. *PloS one.* 2017;12(2):e0170547-e. doi: 10.1371/journal.pone.0170547. PubMed PMID: 28187125.
93. Skelton DA, Young A, Greig CA, Malbut KE. Effects of resistance training on strength, power, and selected functional abilities of women aged 75 and older. *J Am Geriatr Soc.* 1995;43(10):1081-7. PubMed PMID: 7560695.
94. Rikli R, Jones J. Development and validation of a functional fitness test for community-residing older adults. *J Aging Phys Act.* 1999;7:129-61.
95. McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical care.* 1993;247-63.
96. Griffin EW, Mullally S, Foley C, Warmington SA, O'Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav.* 2011;104(5):934-41. Epub 2011/07/05. doi: 10.1016/j.physbeh.2011.06.005. PubMed PMID: 21722657.
97. Cassilhas RC, Lee KS, Venancio DP, Oliveira MG, Tufik S, de Mello MT. Resistance exercise improves hippocampus-dependent memory. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al].* 2012;45(12):1215-20. PubMed PMID: 22930413.
98. Demirakca T, Cardinale V, Dehn S, Ruf M, Ende G. The Exercising Brain: Changes in Functional Connectivity Induced by an Integrated Multimodal Cognitive and Whole-Body Coordination Training. *Neural Plasticity.* 2016;2016:11. doi: 10.1155/2016/8240894.
99. Weng TB, Pierce GL, Darling WG, Falk D, Magnotta VA, Voss MW. The Acute Effects of Aerobic Exercise on the Functional Connectivity of Human Brain Networks. *Brain Plast.* 2017;2(2):171-90. doi: 10.3233/BPL-160039. PubMed PMID: 29765855.
100. Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H, Kim JS, Morris KS, White SM, Wójcicki TR, Hu L, Szabo A, Klamm E, McAuley E, Kramer AF. Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia.* 2010;48(5):1394-406. doi: <https://doi.org/10.1016/j.neuropsychologia.2010.01.005>.

101. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo A, White SM. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Frontiers in aging neuroscience*. 2010;2:32.
102. Bailey DM, Marley CJ, Brugniaux JV, Hodson D, New KJ, Ogoh S, Ainslie PN. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. *Stroke; a journal of cerebral circulation*. 2013;44(11):3235-8. doi: 10.1161/STROKEAHA.113.002589. PubMed PMID: 23963329.
103. Barnes JN, Taylor JL, Kluck BN, Johnson CP, Joyner MJ. Cerebrovascular reactivity is associated with maximal aerobic capacity in healthy older adults. *Journal of applied physiology*. 2013;114(10):1383-7. doi: 10.1152/japplphysiol.01258.2012. PubMed PMID: 23471946; PMCID: 3656423.
104. 157. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, Thomas KN, Williams MJ, Atkinson G. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *The Journal of physiology*. 2008;586(16):4005-10. Epub 2008/07/19. doi: 10.1113/jphysiol.2008.158279. PubMed PMID: 18635643; PMCID: 2538930.
105. van der Kleij LA, Petersen ET, Siebner HR, Hendrikse J, Frederiksen KS, Sobol NA, Hasselbalch SG, Garde E. The effect of physical exercise on cerebral blood flow in Alzheimer's disease. *Neuroimage Clin*. 2018;20:650-4. doi: 10.1016/j.nicl.2018.09.003. PubMed PMID: 30211001.