The Effect of Physical Activity on Aging and Dementia

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Introduction and Research Question

The 2017 Lancet Commission on dementia prevention states that controllable factors are the cause of up to 35% of dementia cases, with one being physical inactivity (Livingston et al., 2017: 2677). The World Health Organization estimates around 2.1 billion people will be aged 60 or older and 426 million will be over 80 years old by 2050 (WHO, 2022). This emphasizes that the world's population is rapidly aging, thus the proportion of individuals living with dementia and other memory deficiency related diagnoses also is potentially facing a drastic increase.

Around 60% of adults do not engage in enough regular physical activity to gain either the physical or cognitive benefits of participation (Tyndall et al, 2018: 221) and 74% of adults do not exercise for at least 30 minutes on multiple days throughout the week. Not only do these numbers impact the adult's lives, but many children are starting to exercise less than in the past, which implicates a potential earlier onset of several diseases and cardiac issues (Hillman, Erickson, Kramer, 2008: 58). Should these trends continue, the country and world will face not only a growing elderly population, but an increasing inactive population at risk for multiple chronic diseases.

Dementia is the 7th highest cause of death among adults and 5th highest cause in adults over 65 (WHO, 2023). There are no current cures for dementia and memory related decline, but there are several treatments to alleviate symptoms in those who are diagnosed. However, these drugs, such as cholinesterase inhibitors, anti-amyloids, glutamate regulators, and orexin receptor antagonists, are often available in a limited capacity and carry intense side effects. Therefore, it is necessary and beneficial to explore other treatments to aid those with dementia.

A commonly expressed sentiment is that exercise is good for not only physical health but also for mental health and well-being. It is generally accepted that regular exercise can improve heart health and that the endorphins released during movement can help fend off depression, but the latest research is now including cognitive function in the benefits of exercise. This paper will attempt to determine if those who engage in regular exercise will have better sustained and long-term memory than those who do not, and if exercise can affect an individual's brain to the extent that development and progression of dementia is impacted. Additionally, it will investigate if

exercise can slow the progress of memory loss in those who already have received a dementia diagnosis.

There are several studies included that both investigate the pre-dementia or healthy control brain and the post-diagnosis brain, which will be helpful in determining the extent of the impact of exercise. Both longitudinal and short-term survey-based studies will be utilized in this analysis. Next, imaging studies will be helpful to see the neural correlates, rather than strictly memory task-based performance or symptomatic diagnosis.

Biomarkers of memory decline

In the discussion about risk for dementia and other memory related pathologies, it is first important to highlight the biomarkers of such diseases. A variety of these will relate to physical activity, but there are also genetic factors and predispositions many individuals have that cannot be impacted.

As an individual ages, it is not uncommon to have lower grade inflammatory markers, such as C-reactive protein (CRP) levels and other cytokines and proteins, in the brain. These can lead to an increased risk of adverse neurological aging and a dysregulation of the blood-brain barrier. Similarly, growth factors, which play a part in neurogenesis and plasticity, decline with aging and impact spatial memory performance. However, these are both biomarkers that exercise and physical activity can have a direct impact on. Those who are more physically active over a lifetime have lower CRP levels, which can decrease the speed of brain aging due to inflammation and increase the growth factor levels, leading to an increase in hippocampal volume and memory functionality (Tyndall et al., 2018: 218).

Other biomarkers include cardiometabolic and genetic risk factors and oxidative stress. Cardiometabolic syndrome (MetS) becomes more common when an individual is inactive, and the syndrome has significant impact on processing speed and memory. This indicates that those with MetS may have an accelerated rate of cognitive decline. For those with MetS, exercise is a preventative mean to many of the risk factors associated with the disease. Oxidative stress can also accelerate the process of aging, but it has been shown that those who are more physically fit have lower impact from oxidative stress levels and higher antioxidant enzymes (Simioni et al., 2018: 17197). The last biomarker is genetic risk. There are a variety of genetic factors that are associated with a predisposition to the development of AD, and it does not appear that physical activity can impact these in any way.

Aging and brain structure

There are several structures which are important to memory functionality. The hippocampus is one of these structures- identified for its role in memory functions such as learning, encoding, and consolidation of information. In healthy adults, it is normal to observe a decrease in hippocampal volume by up to 2% per year due to oxidative stress and inflammation. In adults with dementia, that atrophy rate increases to almost 5% per year (Barnes et al., 2009: 1717). Aerobic exercise has demonstrated that the hippocampus has potential plasticity, as the volume increased in response to a 6-month exercise protocol (Tyndall et al., 2018: 220).

Other regions that shrink in healthy adults include the prefrontal, neostriatal, and cerebellar regions. These regions are responsible for short term memory, motor planning and decision making, and cognitive processing functions respectively. In demented adults, these regions demonstrate atrophy earlier and faster, but the specific rate of atrophy is currently unknown. There are also additional regions indicating brain shrinkage in a symptomatic brain, such as the parietal and occipital cortices and gray matter volume in the prefrontal and medial temporal lobes (Rabinovici et al., 2007: 480). These regions all control factors and functions other than memory, which lend to the other symptoms of aging and dementia.

Benefits of physical activity

Physical activity that regularly increases the heart rate of healthy individuals has been shown to lead to higher volume of gray matter in the brain (Ramanan & Graff-Radford, 2022: 825). Gray matter contains information about memory, emotions, and movement, which indicates why an increased gray matter volume is hypothesized to affect and offset the consequences of memory-related pathologies. Moderate exercise also has evidence supporting its effects on hippocampal nerve growth which, in turn, can support and enhance memory functionality. Therefore, long term physical activity can affect long-tern memory and behavioral hippocampus related memory tasks (Ghloamnezhad, Boskabady, Jahangiri, 2020: 304). These findings are important to the implications of exercise on the lifestyles of those with dementia and at risk for dementia, as there are direct links between activity, memory, and cognitive reserve.

Cognitive reserve is a mechanism of resistance within the brain. It is the term that reflects the brain's ability to complete tasks and resist brain damage, such as neurodegeneration. High cognitive reserve may indicate a better resiliency of the individual to damage or pathology and a slower process of cognitive aging, but this hypothesis is surrounded by discrepancies and skepticism. Cognitive reserve relates to the individual level of susceptibility to disease, which

means there is a difference of severity of the disease at the individual level. This allows for a specific measure of study to determine the overall role of cognitive reserve in dementia progression. Previous research indicates that there may be a causal relationship between activity and the rate of hippocampal atrophy and neural plaque accumulation in health aging (Valenzuela et al., 2008: 2598).

Stern completed a shorter-term study, where almost 600 nondemented elders were grouped based on level of daily activity. Those with higher participation in physical leisure activities had a 38% lower risk of developing dementia than their less active peers (Stern, 2012: 1008). Higher cognitive reserve due to these activities decreased their risk of being diagnosed with dementia by 46%. However, they also found that those with higher cognitive reserve show a more rapid decline once the pathology presents itself. Therefore, those who are more active have a more rapid decline post onset. Since higher cognitive reserve can resist pathology, the decline evidently begins once the pathology is more advanced than someone who presents symptoms of the same pathology earlier.

Lee et al. produced similar results, where they hypothesized that cognitive reserve would have different effects on the progression of memory decline depending on the disease status of the individual. The sample size included those with AD, post-symptomatic pre-diagnosed AD, preclinical AD, and the cognitively unimpaired. Rather than perform physical activity tests, they utilized data from memory tests and the AD Neuroimaging Initiative 3 over a period of four years. Using amyloid and cognitive reserve markers, they compared PET scans for gray matter and cortical thickness to then determine the total volume of gray matter, white matter, and cerebrospinal fluid (TIV). The images were compared over the four years to determine both the level that the CR marker modulated pathology effects and the atrophy value based on the decline in total intracranial volume and thickness of regions of the brain. They then had to compare these results to the disease conversion factor over the four years. In all groups, there was a clear cognitive decline. A higher cognitive reserve indicated a lower conversion rate, meaning that those with higher cognitive reserve progressed through the disease at a slower rate. However, a higher cognitive reserve marker in the brain scans related to a faster decline on the spectrum of the disease severity (Lee et al., 2022: 9).

The conclusions from this study not only validate Stern's findings but expand the evidence, as they utilize the longitudinal brain scans and biomarkers of individuals at different stages of diagnosis or lack thereof. These two studies prove that cognitive reserve, while helpful, also eventually leads to the steep decline of cognitive ability. It is imperative to take these results within

the bigger picture. Should an individual engage in more physical activity, it is highly likely that their cognitive reserve will increase over time. This increase will potentially grant them an increased number of years lived without symptoms, but once these symptoms do present, the individual will decline quicker.

Healthy patient studies

The importance of studying healthy controls cannot be overstated in research of the human brain. A shorter longitudinal study followed 1740 healthy individuals aged 65 and above for 6 years with biennial exams utilizing the Cognitive Abilities Screening Instrument (CASI) to screen for incident dementia (Larson et al., 2006: 74). This study took baseline measurements of cognitive function, exercise frequency, lifestyle characteristics, and physical function like many others, but additionally measured depression and specific risk factors for dementia. After the baseline assessments, participants were split into two groups: those who exercise 3 or more times per week and those who exercise less than 3 times per week.

Over these 6 years, 1185 of the 1740 remained healthy. In the 'highly active' group, the incidence rate of dementia was 13 per 1000 person years. In the less active group, the incidence rate was 19.7 per 1000 person years. As variables from the baseline measurements were added to the model, the incidence rates did not change. The numbers and variables indicate that there is a 32% reduction in risk for developing dementia for individuals who exercise 3+ times per week. The absence of change in risk when other variables are coupled with the statistics from exercise gives extra evidence that there are some factors which may indicate risk more than others.

Additionally, there have been several studies done which vary the time and intensity of the workouts for healthy elderly individuals. The participants go through either MRI scanning or memory tests before and after completion of the study. Cycling for three hours a week for a six-week period improved verbal memory performance, walking at 75% heat rate every day for 40 minutes for 7 weeks improved spatial memory, and moderate intensity aerobic exercise showed increases in the prefrontal and cingulate gray matter volume as compared to low intensity physical activity (Ghloamnezhad, Boskabady, Jahangiri, 2020: 307).

This study goes further to specifically investigate the preventative effects exercise can have on dementia. They found higher intensity exercise has a greater impact than lower intensity in decreasing risk, but only over a certain range. The exercise must fall in the range of 500-2000 calories burned each week, which decreases dementia risk by 10%. This is the first study that suggests a specific parameter for physical activity that is not just time spent in a heart rate zone.

Through these healthy patient studies, it appears that there is a reduction in risk of being diagnosed with dementia that is attributed to the number of hours engaged in working out and the frequency of doing so.

Studies post diagnosis

Another area of relevant study is the implementation of exercise trials among those who are already diagnosed with dementia. Atherton et al. completed a randomized controlled trial, Dementia and Physical Activity (DAPA), to determine the effect of a four month long, intense training program on cognition in around 300 people of the same age diagnosed with mild or moderate dementia. Initially, participants took part in 29 hours of exercise classes which covered a variety of physical activities. After the first four months, they set exercise goals and were expected to complete physical activity on their own.

The exercise group had lower cognition levels at the 12 month follow up than the control group by a mean score of 1.4 on the ADAS-cog score assessment (Lamb et al., 2018: 6). These results demonstrate that the exercise program, added to the usual care of patients, did not slow the cognitive decline of the participants. While it did improve short term physical fitness, there were no improvements in daily living activity or behavioral outcomes.

One of the main factors that differs between this study and the previous and following studies is the level of physical activity. There was no expectation that the individual engaged in exercise before this study, since the only criteria for participation was the ability to walk 10 feet without assistance. Therefore, this study concludes that four months of exercise with an assumption of continued individual activity is not enough to change the progression of dementia and cognitive performance, but it does not nullify the results of studies which look at individuals with a longer history of working out.

From 2016-2018, 80 individuals with mild (54) and moderate (26) dementia participated in a study that had a follow up period continuously over the span of two years. This study by Chen used the previous DAPA study as background but also took note of the short period of exercise. For this study, they considered regular exercise habits of the patients and looked at the ability to predict the outcomes based on an initial physical test (PPF). To be classified into the ‘exercise’ group, patients must engage in an activity producing sweat or labored breathing for over two hours per week (Chen, 2020: 2).

In those who were diagnosed with mild dementia in the exercise group there were positive effects on both cognition and performance. There were no significant differences in fitness or

cognitive performance in those with moderate dementia regardless of the level of physical activity or walking they engaged in. This further indicates that there may be a threshold for positive outcomes, whether it be in time spent exercising over the life or the stage in the progression of dementia.

Longitudinal studies

Najar et al conducted a longitudinal study which followed 800 women over a 44-year period to determine the impact of activity on cognitive health and dementia. Based on a baseline interview, the 800 women were divided into four groups where activity levels ranged from 1, mainly watching television and going to the movies, to 4, which included heavy and intense physical training multiple hours per week. Levels 2 and 3 included light physical activity differing in the hours engaged per week. These activity groups were consistent with the activity the women engaged in prior to joining the study, indicating no major life changes were to be made for this research.

To diagnose dementia, each participant had a neuropsychiatric examination every 5 years during the study, where the DSM-III-R criteria was utilized as the gold standard of diagnosis. Over the observed 44 years, 24.3% of the women were diagnosed with dementia at a mean of 31.5 years post study commencement (Najar et al., 2019: 1323-26). Najar et al conclude that physical activity (groups 2-4) during the women's mid-lives indicated a reduced risk of developing dementia by an average of 70% as compared to group 1.

Another longitudinal study spanning 44 years by Hörder et al. selected 171 women from almost a 1500-person pool to complete maximal fitness testing. The group was then placed into two further groups- medium and high fitness- based on max workload and peak performance numbers.

Over the study's 44 years, the women underwent dementia diagnosis tests every 5 years. 44 women developed dementia at some point during the diagnostic period, with a mean time to onset of 29 years and mean age as 80.5 years. Of the women in the low fitness category, 70% were diagnosed with dementia. Those who were categorized as having high fitness had a mean time of onset 5 years longer than those with medium fitness. Additionally, the mean age of dementia onset was +11 years for the high fitness group (Hörder et al., 2018:1299-1300). They concluded that high fitness decreased the risk of dementia by almost 90% in this longitudinal study

An important clarification of this study is that it studied performance on a maximal fitness test. The authors make the important distinction between physical activity and fitness. This data

utilizes a single instance of cardiovascular fitness to imply lifestyle habits. However, it is assumed that those who regularly engage in physical activity are able to give a higher output on a maximal load test.

Imaging Studies

The following study designs utilize fMRI and PET imaging to determine the effects of physical activity on brain structures and function.

In a 2017 study, 34 adults were split into control and exercise groups for 6 weeks to determine the effect of exercise on a memory test of pair-associate retrieval. The group underwent subsequent fMRI testing during the testing to monitor activation pre and post exercise intervention. One group biked for 3 hours minimum per week for all 6 weeks and the other group did not make any change to their daily routine.

There were no detectable differences between the groups during the memory test, but there were significant differences between the two groups in the activation seen in the fMRI. The specific regions of interest were the left anterior hippocampus and temporal cortex, where there were significantly increased BOLD signals in the exercise group and higher activation during retrieval (Wagner et al., 2017: 73-74). This indicates that there is a potential increased anterior hippocampal activation due to physical activity, which implicates better memory functionality over time.

Another trial put 110 underactive elderly individuals without evidence of dementia through a 52-week exercise program to investigate changes in amyloid levels and hippocampal volume through both PET and MRI scans. Amyloid is an indicator of AD, where increased amyloid allows plaque to form on the brain. As this plaque builds over time, it causes cell death and symptoms of memory loss. They found a 0.8% increase in amyloid over the year in those who went through the exercise regimen, whereas the control reported changes ranged from 1-4% (Vidoni et al., 2021: 12). They found no substantial differences in hippocampal volume over time with exercise. The conclusion from this data is that a year of exercise has minimal influence on amyloid levels and no substantial influence on brain region volume.

The key takeaway from these two studies is the idea that healthy brains may not change much over a year of exercise, but unscreened or symptomatic brains may be impacted in as little as six weeks. There must be additional healthy and unhealthy brain scans in this area of study to determine the timing and effect of exercise on cognitive function.

Conclusion

Most studies put forth compelling evidence for long term exercise as a treatment for and protection against the symptoms of dementia and cognitive decline. However, the secondary effects on psychological benefits and behavioral outcomes remain mixed (Lewis et al., 2020: 123-124). There is both a need for exercise over a lifetime to gain the benefits and more research in this area to determine the shortest period of exercise an individual can engage in to reap the benefits for their brain.

Studies on cognitive reserve conclude that exercise increases cognitive reserve and therefore is successful in fending off symptoms of dementia, but that higher cognitive reserve will increase the rate of decline post diagnosis. Several longitudinal studies were successful in finding significantly decreased risk of developing dementia through exercise, with the risk decreasing by anywhere between 70-90%. The short-term brain imaging studies did not come to the same conclusions. They find that exercise and physical activity may slow the rate of both amyloid accumulation and hippocampal shrinkage, but there must be further research done to determine the significance of these decreased rates.

There are currently no negative effects stemming from exercise in those with dementia. This indicates that there are only positive outcomes from physical activity, in those with and without dementia or Alzheimer's. At present, the best recommendation is simply to begin engaging in or increase engagement with physical activity.

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