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Exercise and Preventing Dementia in Older Adults

Valerie K. Snelling
University of North Dakota

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By

Valerie K. Snelling, MS, CCC-SLP, PA-S

Master of Science, Minnesota State University Moorhead, 2013

Bachelor of Science, Minnesota State University Moorhead, 2011

Contributing Author: Dr. Jeanie McHugo, PhD, MPAS, PA-C

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Abstract

Dementia is a devastating diagnosis for millions of individuals and the prevalence is projected to increase significantly in the next 30 years. According to the Centers for Disease Control and Prevention (2019), there are over five million individuals aged 65 and over living in the United States with dementia. That number is estimated to increase to 14 million by 2060. The impact of the increasing prevalence of dementia is significant. Because dementia is a complex disease caused by over 50 underlying health conditions, finding effective treatments for the disease is difficult. This makes prevention of dementia extremely important. The purpose of this literature review is to analyze if exercise prevents dementia in older adults. Studies were included if they analyzed physical activity with the onset of dementia or changes in various cognitive abilities. This literature available to date indicates that exercise is an effective measure to prevent dementia in older adults.

Keywords: Dementia prevention, exercise, physical activity, preventing dementia, modifiable risk factors, older adults

Introduction

According to the Centers for Disease Control and Prevention (2019), there are over five million individuals aged 65 and over living in the United States with dementia. That number is estimated to increase to 14 million by 2060. Dementia is the term used to describe changes in memory, language, problem-solving and other cognitive abilities that are significant enough to interfere with daily living. Dementia is not a single disease, and it is caused by multiple diseases that cause damage to or lose of nerve cells and their connections in the brain. The increase in prevalence of dementia will greatly impact the burden of family members, caregivers, healthcare workers, and cost to support individuals living with dementia. The Alzheimer's Association (2023) estimated that an additional 1.2 million direct care workers will be needed between 2020 and 2030. In addition, the number of health care providers who treat individuals with dementia will need to almost triple for effective care to be provided for the estimated increase individuals with dementia by 2050. Currently, the total lifetime cost of care for an individual living with dementia is $392,874. This number does not include time provided by unpaid caregivers. Individuals with dementia spend more time in skill nursing facilities and have more home health care visits per year compared to older individuals without dementia. In addition, individuals with dementia have twice as many hospital stays per year compared to older individuals without dementia. The impact of the increasing prevalence of dementia is significant. Because dementia is a complex disease caused by over 50 underlying health conditions, finding effective treatments for the disease is difficult. Treatment for dementia is multi-faceted, including drugs to slow the progression and treat specific symptoms, therapies to maintain function, and caregiver training to support individuals with dementia. Treatment options are continually being researched; however, treating dementia remains a large challenge. Because treatment is difficult and dementia has a significant impact on individuals, prevention has become a focus of research and education.

Statement of the Problem

Dementia is a devastating diagnosis for millions of individuals and the prevalence is projected to increase significantly in the next 30 years. With less than 1% of individuals diagnosed with dementia having a specific genetic mutation, research has shown lifestyle and coexisting medical conditions play a significant role in risk of developing dementia. As stated above, treating dementia is challenging, making prevention extremely important. To help strengthen education for prevention of dementia, research on modifiable risk factors, like exercise, is vital to alleviate the increase in the prevalence of dementia diagnosis.

Research Questions

Does exercise reduce the risk of developing dementia in older individuals?

Methods

A literature review was performed utilizing electronic search databases, Embase, PubMed, and CINAHL. Keywords and mesh terms were used to obtain a group of peer reviewed research studies analyzing and discussing the effects of exercise on preventing dementia in older adults. Keywords and mesh terms used were exercise, dementia prevention, physical activity, modifiable risk factors of dementia, and APOE genotype. The search revealed over 6,500 studies. There were multiple studies excluded due to the design being a meta-analysis or an article discussing hypotheticals based on previous research. Studies over 10 years old were also excluded. Other studies were excluded due to the population of the study including individuals with diagnosed dementia. Inclusion criteria for studies were study designs being prospective or retrospective, studies that analyzed unique data sets, and those that included participants without a diagnosis of dementia at the onset of the study. Nine studies met the final criteria.

Literature Review

Type and Amount of Exercise

Kuo et al. (2022) conducted a prospective cohort study utilizing the UK biobank to analyze the association of grip strength and walking pace with the risk of incident dementia. The UK biobank is a population-based database of more than 500,000 individuals ranging in age from 40-69. Participants from the databank were recruited from 2005-2010. Individuals were invited to attend centers located throughout England, Scotland, and Wales for baseline assessments. Baseline assessments involved gathering clinical, biochemical, and genetic information from touchscreen questionnaires, physical measures, sample assays, genotyping, and electronic health records. Individuals who were diagnosed with dementia prior to the start date of baseline measurements and those diagnosed with cardiovascular disease prior to baseline measurements and during the follow-up were excluded from the study. Of the 502,264 participants from the initial sample, 68% were eligible for the study. Demographic information was gathered during the initial assessment, including age, gender, ethnicity, education, and body weight. BMI was calculated and classified using the WHO's criteria: < 25 = underweight and normal weight, 25 to < 30 = overweight, and ≥ 30. The following information about the individuals included in the study were self-reported: educational level, smoking status, alcohol intake, diagnosis of diabetes, and current medications. Metabolic equivalent (MET) minutes/week was used to denote physical activity. The International Physical Activity Questionnaire was used to determine the amount of physical activity individuals completed. The Townsend Deprivation Index was utilized to classify individuals into three categories: high, middle, and low. Blood pressure values were calculated using two different sitting measures with hypertension being defined by the AHA 2017 guidelines of blood pressure readings of systolic ≥ 140 mm Hg and diastolic ≥ 90 mm Hg. The genetic database was utilized to determine Apolipoprotein E status (Kuo et al., 2022).

Grip strength and walking pace were measured at baseline. Grip strength was determined by using a hydraulic hand dynamometer. Both left- and right-hand grip strengths were measured. Grip strength was reported in both absolute units (kilograms) and relative units (kilograms divided by body weight). These measurements were placed in age and sex specific groups for comparison purposes. Walking pace was determined by a self-reported questionnaire that asked the participants to describe their usual walking pace and provided three choices: slow pace (< 3 mph); average/steady pace (3-4 mph), or brisk pace (> 4 mph) (Kuo et al., 2022).

This study aimed to identify individuals that developed dementia any time after baseline measures were obtained, those lost to follow-up, an update from a healthcare provider indicating a dementia diagnosis had been given, or a death certificate listing dementia as the underlying/contributing cause of death. This information was found in the UK biobank which has well established reliability. The researchers looked at all-cause dementia (ACD) and it's two major subtypes, Alzheimer's Disease (AD) and Vascular Dementia (VaD) (Kuo et al., 2022).

This study completed multiple statistical analyses on relationships between baseline characteristics and individuals with and without incident dementia. The study utilized chi-square tests or one-way analysis of variance (ANOVA) to analyze these relationships. The study also investigated the longitudinal relationships of grip strengths, walking pace, and incident dementia as the time variable. The study utilized cox-proportional hazard models to assess these longitudinal relationships. They used three different models to analyze the information: Model

1-the data unadjusted; Model 2-adjusted for sociodemographic factors of age, sex, ethnicity, education, BMI, and Townsend Deprivation Index, and lifestyle factors of smoking alcohol MET minutes/week, and sedentary hours/day; Model 3-adjusted for disease related factors of hypertension, diabetes, and APOE4 status. R software version 4.1.0 and GraphPad version 8.00 were used for statistical analyses and figure preparation. The significance threshold was set at $p < .05$ (Kuo et al., 2022).

Of the individuals included in the study, 0.7% (2,424) were identified to have ACD during an average of 8.5 +/- 2.68 years of follow-up. 52% (1,251) of those individuals were diagnosed with AD and 13% (312) were diagnosed with VaD. They found those with dementia were likely to be older, female, lighter in body weight, previous smokers, infrequent drinkers, socioeconomically deprived, less physically active, less educated, and have a higher prevalence of hypertension, diabetes, and be APOE4 positive. The mean age for individuals with no incident dementia was 55.91 compared to a mean age of 63.67 with dementia ($p < .001$). In individuals with no prior alcohol use, 4.3% did not develop dementia compared to 8% who did develop dementia ($p < .001$). Of the individuals who were categorized in the high category of the Townsend Deprivation Index, 20.9% developed dementia compared to 18.7% who did not. The average BMI of those with no incident dementia was 27.26 compared to 27.02 of those who developed dementia ($p = .012$). The average MET minutes/week for individuals without dementia was 2,666.09 compared to 2,628.41; however, this was not statistically significant ($p = .496$). For education level, 162,606 individuals with no incident dementia had a higher education compared to 895 with dementia ($p = .017$). Of individuals who previously smoked, 33.3% had no incident dementia and 39.8% developed dementia ($p < .001$). Females comprised 55.4% of the individuals with dementia ($p = .004$). In individuals with hypertension, 57%

developed dementia and 8.8% of individuals with diabetes developed dementia compared to 4% of individuals with diabetes with no incident dementia ($p < .001$). The study delineated APOE4 status by 0 alleles, 1 allele, or 2 alleles ($p < .001$). A high percentage, 71.7%, of individuals with 0 alleles did not develop dementia and 43.3% with one allele did develop dementia. Interestingly, the percentage, 11.9%, of those with 2 alleles who developed dementia was lower than the percentage of those who developed dementia with 1 allele, but it was still greater than those with 2 alleles with no incident dementia. Those with dementia had lower mean values of absolute and relative grip strength and slower walking pace. Grip strength showed an inverse association with all dementia types. A 5 kg increment of absolute grip strength was associated with 14.3%, 12.6%, and 21.2% lower risk of ACD, AD, and VaD, respectively. Like grip strength, walking pace had an inverse relationship with diagnosis of dementia. Slow walking pace increased risk of all dementia types when compared to average walking pace. There was no association that brisk walking pace specifically decreased the risk of developing dementia. Of the individuals in the slow walking pace group, 14% developed dementia and 6.6% did not, and for those in the average walking pace group, 53.4% developed dementia and 52.8% did not ($p < .001$). Absolute grip strength for those who developed dementia was 27.10kg compared to 30.35kg for those with no incident dementia ($p < .001$) (Kuo et al., 2022).

This study has many strengths. The large number of participants and length of follow-up are two of the biggest strengths. In addition, the study analyzed many characteristics of each individual for statistical associations with developing dementia. They also adjusted certain data for variables that could sway the data one way or another and found that the results held true. The information was presented in line graphs, bar graphs, and charts with data. In addition, the different types of dementia were analyzed with all variables studied (Kuo et al., 2022).

One potential limitation with the study is that there was no set timeframe for how long they followed individuals in the study. This allowed room for new medical diagnoses that were not known or a change in economic status to occur influencing the outcomes of the study. Another limitation was the self-reported walking pace. Individual's perception of their own walking pace could vary greatly. The researchers did not conduct their own assessments for dementia leading to the potential of variation in criteria for diagnosis among participants (Kuo et al., 2022).

Koh et al. (2020) conducted a longitudinal, retrospective study analyzing the association of physical exercise and cognitive status in middle and older aged Koreans. The study utilized data from the 2006-2018 Korean Longitudinal Study of Aging (KLoSA). The KLoSA randomly selected individuals aged 45 and older. They implemented a stratified, multi-stage area probability sampling method to obtain a sample that was representative of the nation for individuals aged 45 years and older. Information was collected using the Computer Assisted Personal Interviewing (CASPI) technique during face-to-face interviews. Individuals who scored lower than 19/30 on the Korean Mini Mental State Exam (K-MMSE) were excluded from the study, as well as individuals who were unable to complete one or more activity of daily living. Other individuals were excluded due to missing values regarding depressive symptoms. There was a total of 8,888 individuals included in the baseline study population.

The outcome of this study was cognitive function as measured by the K-MMSE. The max score on the K-MMSE is 30 and a score of 24/30 indicates normal cognitive function, 20-23/30 indicates cognitive decline, and ≤ 19/30 indicates dementia. The intervention for this study was physical exercise. Physical exercise for this study was based on total exercise time per week (minutes per week), duration per exercise (minutes per exercise), and exercise frequency per week (days per week). This information was gathered by KLoSA via individuals answering a standardized question regarding exercise type, frequency, and duration. Of the individuals included in the study, 58.2% (5,173) did not participant in regular exercise. Individuals who exercised regularly were put into quartiles with the ranges set at 120, 240, and 420 minutes per week. The quartiles had the following breakdown of participants: 676 (7.6%) individuals were categorized into the Q1, 1,157 (13.0%) into the Q2, 908 (10.2%) into the Q3, and 974 (11.0%) into the Q4 group (Koh et al., 2020).

This study utilized a generalized estimating equation (GEE) model to analyze the relationship between physical exercise and MMSE scores. The GEE model was used, because it considers time variation and correlations between repeated measurements that are found in longitudinal studies. Age, educational level, and marital status were analyzed as subgroups. All p-values were two-tailed, and the level of significance was set at .05. The GEE analysis on the association between MMSE scores and physical exercise were run in two different ways. Model one included unadjusted data and model two used adjusted data (Koh et al., 2020).

MMSE scores increased in both models as total exercise time per week increased. Model one revealed Q1 group (β: 0.5261, $p \leq .0001$), the Q2 group (β: 0.3244, $p \leq .0001$), the Q3 group (β: 0.5815, $p \leq .0001$), and the Q4 group (β: 0.5626, $p \leq .0001$) showed better MMSE scores than participants who did not exercise. Superior scores were revealed in model two in the quartiles of individuals who exercised compared to those who did not exercise [Q1 (β: 0.3523, $p \leq .0001$), Q2 (β: 0.2011, $p \leq .0001$), Q3 (β: 0.4075, $p \leq .0001$), and Q4 groups (β: 0.3144, $p \leq .0001$)] groups. There was a positive correlation in duration of minutes per exercise and MMSE scores in model 1: short (≤ 59) β: 0.2840 $p \leq .0001$, moderate (60-119) β: 0.5742 $p \leq .0001$, and long (≥ 120) β: 0.7321 $p \leq .0001$. Model two showed similar results for short and moderate exercise groups, however the long exercise group had lower scores compared to the short and moderate groups (short (≤ 59) β: 0.2903 $p \leq .0001$, moderate (60-119) β: 0.3576 $p \leq .0001$, and long (≥ 120) β: 0.2662 $p \leq .0001$). In addition, increased frequency of exercise in days/week revealed a positive correlation with MMSE scores in model two (moderate (1-3 days) β: 0.2713 $p \leq .0001$, frequent (4-7 days) β: 0.3552 $p \leq .0001$) (Koh et al., 2020).

Koh et al. (2020) found that there is a positive relationship between physical exercise and cognitive scores on the MMSE in Korean middle-aged and elderly individuals without dementia. The data clearly revealed that individuals who completed regular physical exercise scored higher than those who did not. This study did not find a dose-based improvement in MMSE as Q3 scored the highest on the MMSE followed by Q1, Q4, and Q2 groups.

This study has many strengths, including the study design, large number of participants, and length of time. The large number of participants allows for greater generalization to the population studied. In addition, variables of sex (male or female), age (45–64 years or 65 years or above), age, household income (quartiles), educational level (high school or below or college or above), marital status (single or separated, or married and cohabiting with spouse), depressive symptoms (no or yes), chronic diseases (none, one, or two or above), smoking status (no or yes), perceived health status (poor or fair), and region (rural areas, small to medium sized cities, or large cities) were assessed to adjust for influence on results. The use of a standardized cognitive assessment that is widely used and understood by healthcare professionals is another strength (Koh et al., 2020).

Limitations of this study include lack of regulation in the type of exercise and level of activity. Activity level was a self-reported measure which leaves room for significant variation. In addition, the length of time an individual has been completing the reported exercise routine was not discussed. This could have accounted for the dose-based conclusions not being found (Koh et al., 2020).

Baek et al. (2021) conducted a prospective study investigating the effects of physical activity in the form of Taekwondo training on physical characteristics and risk factors of dementia among elderly women with depression. Participants were recruited for this study via ads on bulletin boards in various welfare centers for senior citizens. Eligibility criteria for this study included appendicular skeletal muscle mass index (ASMI) ≤ 5.7 kg/m2 and geriatric depression scale-Korea (GDS–K) ≥ 14-point. Individuals were screened using the Korean dementia screening questionnaire (K-DSQ). A score of ≥ 6 indicates a high probability of dementia. A total of 24 participants were recruited for this study. A pilot test completed previously indicated that each study group needed to have at least 12 participants. Participants were randomly assigned to an exercise group or a control group. The mean of the characteristics of the participants in the exercise group are as follows: age = 72.55, ASMI = 5.34 kg/m^2 , GDS-K = 15.64, K-DSQ = 5.73. The mean of the characteristics of the participants in the exercise group are as follows: age = 72.40, ASMI = 5.55 kg/m^2, GDS-K = 16.00, K-DSQ = 5.90.

The intervention in this study was a Taekwondo training program consisting of 12 weeks with 60-minute sessions and three sessions per week. This program was designed to improve agility, equilibrium, coordination, power, speed, and reaction time. Participants were instructed to complete multiple Taekwondo moves specifically designed to improve the areas listed. The workouts included a warm-up and a cool-down. Participants were instructed to continue their normal diet throughout the 12-week study. The measures for physical function, physical characteristics, and dementia risk factors were assessed at baseline and after 12 weeks. The following were measured for functional fitness: hand grip strength, hand grip strength/weight, 4-

m gait speed, 3-m timed up and go (TUG), figure-of-eight track, 30s chair stand, sit-and-reach. The following physical characteristics were measured: body weight, body mass index, percent fat, ASMI, systolic blood pressure, diastolic blood pressure, GDS-K, positive items, negative. Dementia risk factors that were measured are as follows: total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), free fatty acid (FFA), K-DSQ, Irisin, brain-derived neurotrophic factor (BNDF), and β-amyloid (Baek et al., 2021).

For statistical analysis, a two-way ANOVA was utilized to examine interactions between time and group and differences between groups. A Pearson's correlation coefficient was used with a statistical significant set to $p < .05$ to determine the correlation between each factor. The changes in functional fitness between groups at baseline and 12 weeks were analyzed and there were significant interactions found for hand grip strength (F = 11.426, $p < .01$), hand grip strength/weight (F = 13.114, $p < .01$), 4-m gait speed (F = 108.251, $p < .001$), 3-m TUG (9.483, $p < .05$), and figure-of-eight track (F = 10.027, $p < .05$). For the changes in physical characteristics prior to and after 12 weeks of the Taekwondo program, between-group and between-time interactions were found, including body fat percentage (F = 9.733, $p < .05$), ASMI (F = 16.647, $p < .01$), systolic blood pressure (F = 11.864, $p < .01$), diastolic blood pressure (F = 24.234, $p < .001$), GDS-K (F = 29.110, $p < .001$), and positive items (F= 8.027, $p < .05$). Between-group and between-time interactions for changes in dementia risk factors between before Taekwondo training and after 12 weeks in the program were found for TC (F = 31.936, $p < .001$), TG (F = 23.761, $p < .01$), LDL-C (F = 25.636, $p < .01$), HDL-C (F = 21.890, $p < .01$), FFA (F = 9.871, $p < .05$), adiponectin (F = 17.272, $p < .01$), arteriosclerosis index (F = 27.408, p

< .01), K-DSQ (F = 19.377, $p < .01$), β-amyloid (F = 19.314, $p < .01$), and BDNF (F = 9.854, $p < .05$) (Baek et al., 2021).

This study found that the 12-week Taekwondo training program improved functional fitness which led to an improvement in the depression and physical characteristics of the participants. The data also revealed a correlation with dementia risk factors based on the improvement in cognitive functions and the reduction of the β-amyloid levels (Baek et al., 2021).

One of the major strengths of the Baek et al. (2021) study is the robust statistical data. This study utilized a two-way ANOVA analysis to identify specific variables that are key players in improved physical and cognitive performances. In addition, data was gathered utilizing standardized, well studied methods that provided objective data versus relying on self-reported measures. This study also developed and implemented a unique physical activity program and gathered information pre and post intervention. There was also a control group to compare scores over 12-weeks to strengthen the conclusion that the intervention resulted in the changes in outcomes. The groups were randomly assigned, and the characteristics of each group pre-intervention were compared statistically to account for any major discrepancies that may have impacted the outcomes.

One limitation of this study was the small sample size and specific population studied making generalization difficult. This also makes it difficult to say with certainty that this specific training program is superior to other forms of physical activity in producing the desired outcomes. Another limitation of this study was the short period of time that the individuals completed the program, as well as no follow-up measures to see if these results had an impact long term on physical function and risk of dementia (Baek et al., 2021).

Most Important Modifiable Risk Factors for Dementia Prevention

Nichols et al. (2022) completed a randomized clinical trial investigating if mindfulness-based stress reduction (MBSR), exercise, or a combination of both improve cognitive function in older adults. The study utilized a 2x2 factorial randomized clinical trial conducted at Washington University in St. Louis and University of California, San Diego. The study had a total of 585 participants aged 65-84. The participants had a mean education level of 16.2 years and 72.5% were women, 0.3% were American Indian 4.6% were Asian, 6.7 % were Hispanic/Latino, 11.8% were black, and 81.5% were White. Inclusion criteria included self-reported age-related changes in cognitive function and being cognitively intact. Age-related changes in cognitive function were determined by potential participants answering yes to a question of whether they had noticed trouble with their memory or centration, and individuals were determined to be cognitively intact if they scored less than 10 on the Short Blessed Test (≥ 10 suggests cognitive impairment consistent with dementia). Exclusion criteria included neurodegenerative diseases, not sedentary, current meditation practice or cognitive training, medication conditions that would indicate a shortened lifespan, prohibit safe participation in the interventions, or interfere with study assessment, and non-fluent English-language speaker. Individuals were randomized in a 1:1:1:1 ratio into the following groups: MBSR, exercise, combined MBSR and exercise, and health education (control). Investigators and participants were not informed of the group assignments.

The interventions for this study included MBSR alone, exercise, and MBSR plus exercise, and health education (placebo). Each intervention was conducted for a total of 18 months with the first 6 months considered an acute phase and the last 12 months being maintenance. The MBSR intervention started with weekly 2.5-hour classes for 8 weeks and a half day retreat, followed by monthly meetings for the remainder of the intervention period of 18 months. The meetings provided instruction in mindfulness meditation and exercises. Participants were given a goal of completing 60 minutes of daily at home practice utilizing *A Mindfulness Based Stress Reduction Workbook*. The exercise intervention started with 1.5-hour classes conducted by an instructor at a fitness facility twice weekly for the first 6 months followed by once-a-week classes during the 12-month maintenance period. Exercise classes included aerobic exercise, resistance training, and functional exercises. Participants were also given a home exercise program with instructions to complete a combined total of 300 minutes of exercise between instructor lead classes and home exercise. The individuals in the intervention group of both MBSR and exercise underwent both programs as described previously. The health intervention (control) group was designed to control for nonspecific factors of the study and expectancy. The intervention for this group mirrored the protocol for the MBSR intervention group for group setting, class time, frequency of sessions, and attention to weekly assignments; however, no goals were assigned, and they utilized the book *Living a Healthy Life with Chronic Conditions* with information on mindfulness and exercises omitted. Instructors were monitored for consistency of instruction delivery via video recording and surveys, and participants were monitored for attendance to group sessions and completion of home-based programs via surveys (Nichols et al., 2022).

Primary outcomes measures were obtained for episodic memory and executive function in the form of composite scores at 6 months and again at 18 months. The composite scores were calculated from neuropsychological test batteries completed at 0, 3, 6, and 18 months. Testing for memory included immediate and delayed recall of a 16-item word list and 2 paragraphs, as well as the Picture Sequence Memory Test from the National Institutes of Health (NIH) Toolbox. To assess executive functioning, the following tests were used: Dimensional Card Test, Flanker

Inhibitory Control and Attention Test, and List Sorting Working Memory Test from NIH Toolbox, as well as computerized tests of the Consonant-Vowel Odd-Even Switching test, the Sustained Attention to Response Test, and the Stroop Test (Nichols et al., 2022).

Secondary cognitive outcome measures of left and right hippocampal volume and left and right DLPCF surface area and cortical thickness were obtained by high resolution TI-weighted MRIs at 0, 6, and 16 months. Scores of the Revised Observed Tasks of Daily Living and the Quality of Life in Neurological Disorders Cognitive function measures were also obtained as secondary cognitive outcomes (Nichols et al., 2022).

To measure effectiveness of outcomes, the change in composite scores from baseline to 6 months in the randomized groups was compared to those not receiving the intervention (i.e., MBSR vs no MBSR). A Bonferroni-adjusted 2-tailed significance level of .025 was used for each of the primary outcome measures of episodic memory and executive functions. Effect sizes with 95% Confidence Intervals (Cis) for 6- and 18-month effects for all primary and secondary outcomes were computed. When comparing participants' scores in the primary outcomes at the 6 month interval for individuals with and without MBSR, there were no significant differences: memory composite score, 0.44 vs 0.48; mean difference, –0.04 points [95% CI, –0.15 to 0.07]; $p = .50$; executive function score, 0.39 vs 0.31; mean composite difference, 0.08 [95% CI, –0.02 to 0.19]; $p = .12$. There was also no significant difference in comparison of the primary outcome scores in the groups with vs without exercise: (memory composite, 0.49 vs 0.42; mean difference, 0.07 points [95% CI, –0.04 to 0.17]; $p = .23$; executive function composite, 0.39 vs 0.32; mean difference, 0.07 points [95% CI, –0.03 to 0.18]; $p = .17$). Results for secondary outcomes for the variables of episodic memory and executive function revealed no significant differences at 18 months. Results for the secondary memory outcome are as follows: (MBSR vs

no MBSR: 0.61 vs 0.53; mean difference, 0.08 [95% CI, –0.04 to 0.19]; p = .18; exercise vs no exercise: 0.55 vs 0.59; mean difference, –0.04 [95% CI, –0.15 to 0.07]; p = .47). Results for the secondary executive function outcomes were as follows: (MBSR vs no MBSR: 0.27 vs 0.31; mean difference, –0.04 [95% CI, –0.15 to 0.07]; p = .44; exercise vs
no exercise: 0.28 vs 0.29; mean difference, –0.01 [95% CI, –0.12 to 0.11]; p = .93) (Nichols et al., 2022).

Additional secondary outcomes of MRI measurements and additional cognitive components did not show any significant improvement. For hippocampal volume at 6 months, there were no significant effects from intervention (MBSR vs no MBSR: difference, –3.46 mm3 [95% CI, –14.27 to 7.34]; p = .53; exercise vs no exercise: difference, 3.04 mm3 [95% CI, –7.76 to 13.85]; p = .58), but at the secondary 18 month interval, there was actually a significant decrease in hippocampal volume in the MBSR group vs no MBSR (difference, –20.16 mm3 [95% CI, –33.88 to –6.44]; p = .004). There was not a significant change in the exercise vs no exercise groups for hippocampal volume: exercise (difference, –6.26 mm3 [95% CI, –19.98 to 7.46]; p = .37). For DLPFC surface area, no significant intervention effects were seen at 6 months (MBSR vs no MBSR: difference, 22.71 mm2 [95% CI, –22.95 to 68.36]; p = .33; exercise vs no exercise: difference, –17.18 mm2 [95% CI, –62.83 to 28.48]; p = .46) or at the 18 month interval (MBSR vs no MBSR: difference, 25.35 mm2 [95% CI, –23.18 to 73.88]; p = .31; exercise vs no exercise: difference, 21.11 mm2 [95% CI, –27.41 to 69.64]; p = .39). There were no significant intervention effects on cortical thickness (MBSR vs no MBSR: difference, –0.01 mm [95% CI, –0.02 to 0.01]; p = .37; exercise vs no exercise: difference, 0.01 mm [95% CI, 0.00-0.02]; p = .21) at 6 months or 18 months (MBSR vs no MBSR: difference = –0.01 mm, [95% CI, –0.02 to 0.00], p = .10; exercise vs no exercise: difference, –0.01 mm [95% CI, –0.02

to 0.00]; $p = .09$). Additionally, there were no significant effects on secondary cognitive outcomes of Observed Tasks of Daily Living and Neurological Disorders Cognitive Function score for the intervention groups (Nichols et al., 2022).

Because there was no significant intervention effect when comparing MBSR vs no MBSR and exercise vs no exercise, a 4-group analysis of MBSR alone, exercise alone, combined MBSR and exercise, and health education was completed. There was no significant improvement with MBSR combined with exercise compared with MBSR only, exercise only, or health education (Nichols et al., 2022).

The results of this study revealed that exercise, mindfulness training, or a combination of exercise and mindfulness training do not improve episodic memory or executive functions in individuals with subject cognitive concerns. This study does not support the use of exercise and/or mindfulness training for older adults to improve cognition if subjective cognitive concerns are present (Nichols et al., 2022).

Strengths of the Nichols et al. (2022) study include the design, length, number of participants, and analysis of the results. This study utilized randomized intervention groups and a control group to help control for variables amongst the groups that may have influenced the results. In addition, the individuals completing the various assessments on the subjects in the study were blinded to the groups for an additional layer of controlling for variables. The results of this study were analyzed by comparing the composite scores for the primary and secondary outcomes for the intervention groups of exercise vs no exercise, MBSR vs no MBSR, as well as a four-way analysis comparing the exercise only group, MBSR only group, exercise plus MBSR group, and health information group. This extensive analysis of the data helps improve the confidence in the conclusions of this study. The large data set strengthens the confidence of the results. One limitation of this study is that it only followed individuals for 18 months. Another limitation was only including individuals with self-reported cognitive changes and not including individuals without any self-reported cognitive changes.

Sun et al. (2023) conducted a prospective cohort study investigating the relationship between leisure-type sedentary behavior and the risk of dementia incidence and mortality, as well as the effect on dementia risk when sedentary behavior was replaced with physical activities. Further, they studied the impact of replacing sedentary behavior with exercise in individuals with different APOE genotypes. Data for this study was obtained through the UK biobank. The UK biobank is a cohort study of approximately 500,000 community-dwelling adults across the UK aged 37-73 years. Individuals from the biobank who withdrew from follow-up, had a physician-diagnosis of dementia at baseline or within the first 2 years of the study, and those missing information on leisure-type sedentary behaviors were excluded from the study. The main analysis included 397,519 individuals with 81% (397,519) having an APOE genotype.

The intervention in this study was physical activity replacing leisure type sedentary behavior. Information on individual's leisure time sedentary behaviors and physical activity was gathered by completion of a standardized questionnaire based on the International Physical Activity Questionnaire form. Leisure-time sedentary behaviors were driving, computer use outside of work, and watching TV. Participants were asked to report time spent doing leisure time activities and these were categorized into < 5 h/day, 5-8 h/day, and > 8 h/day. This questionnaire was repeated in three follow-up surveys and the correlation between baseline and repeated surveys was relatively high (Spearman r = 0.642, 0.565, and 0.519, respectively, all $p < .001$). Information regarding physical activities performed at home and during leisure time were separated into categories based on type of activity: (a) walking for pleasure; (b) light do-it-yourself (DIY) activity (e.g., pruning, watering the lawn); (c) heavy DIY activity (e.g., weeding, lawn mowing, carpentry, digging); (d) strenuous (defined as inducing sweat and hard breathing) sports; and (e) other exercise (e.g., swimming, cycling, aerobics, bowling). Information was gathered on the average frequency and duration of each activity performed during the previous four weeks (Sun et al., 2023).

The primary outcomes of this study were incident dementia and dementia related death. Secondary outcomes were Alzheimer's Disease (AD) and vascular dementia (VD). APOE genotype was obtained from genetic information previously reported in the UK Biobank. The following covariates were also analyzed to account for potential confounding effects: age, sex, ethnicity, education, employment status, Townsend index reflecting socioeconomic status, smoking status, alcohol consumption, healthy diet, body mass index, total cholesterol, systolic blood pressure, diabetes, broad depression, sleep duration, genetic kinship to other participants, and cognitive function (Sun et al., 2023).

The Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) for the association of leisure time sedentary behavior and dementia incidence and mortality. The model was adjusted for the covariates discussed above. Next, the likelihood ratio test was utilized to compare the interaction analysis between leisure time sedentary behavior and APOE genotype category. Secondary outcomes were analyzed to investigate if sex, age, BMI, and economic status modified the association between leisure time sedentary behaviors time and dementia occurrence. To analyze the effect of substituting an equal time sedentary behaviors with an equal time of physical activity, an isotemporal substitution model was utilized. The isotemporal substitution model was assessed individually according to sex, age, BMI, economic status, and APOE genotype (Sun et al., 2023).

After two years of follow-up, 6,904 all-cause dementia cases (38% AD, 20% VD) were found and 2,115 deaths due to dementia. After adjusting for the included covariates, increased leisure sedentary time was significantly associated with a higher risk of both dementia incidence and mortality (per 1 SD, HR = 1.06, 95% CI:1.03-1.08 and HR =1.07, 95% CI: 1.03-1.12, respectively). When comparing participants who had the least amount of sedentary time (> 5h/day) to those with 5-8 h/day and >8 h/day, the risk of incident dementia was significantly higher (5-8 h/day: HR = 1.07, 95% CI: 1.02-1.13, >8 h/day: HR = 1.25, 95% CI: 1.13-1.38) (*p* for trend < .001). Similarly, dementia related deaths were significantly increased in those with sedentary behavior >8h/day (HR = 1.35, 95% CI: 1.12-1.61) (*p* for trend = 0.014) (Sun et al., (2023).

When analyzing the effect of replacing 30 min/day of sedentary behaviors with an equal amount of time of physical activity, the risk of incident all-cause dementia, AD, and VD was significantly decreased (by 6%, 5%, and 7%, respectively). In addition, mortality from dementia, AD, and VD were also significantly decreased (by 9%, 6%, and 14%, respectively). The effect of substituting physical activity for sedentary behaviors appears to be more significant among APOE carriers (HR = 0.93, 95% CI: 0.86-1.00 and HR = 0.81, 95% CI: 0.73-0.91 for AD incidence; HR = 0.79, 95% CI: 0.63-0.99 and HR = 0.76, 95% CI: 0.61-0.94 for AD mortality). Analysis was also completed on the intensity of physical activity substituted for sedentary behaviors. They found that substituting 30 min/day of sedentary behaviors with an equal amount of time spent doing light DIY (such as pruning or watering the lawn) was associated with a lower risk of dementia incidence and mortality (12% and 14%, respectively) (Sun et al., (2023).

This study found that longer periods of sedentary behaviors were associated with a higher risk of dementia incidence and mortality. In addition, they found that replacing 30 min/day of sedentary behavior time with equal physical activity significantly reduced the risk of dementia incidence and mortality from dementia (Sun et al., 2023).

One of the biggest strengths of the Sun et al. (2023) study was the robust statistical analysis strengthened by the large number of participants allowing for greater generalization. The design study was prospective which is also a strength. The data gathered was obtained from standardized questionnaires improving the validity of the data. This study categorized responses to questions about covariates with specificity adding to the strengths of the associations found. This study looked at both the risk of dementia incidence and mortality over a 12-year period leading to results that are promising in dementia prevention in the real-world. Also, this study looked at both the risk of incident dementia and dementia related mortality, and if there was an association between physical activity and reduction in risk of incident dementia and dementia related mortality. Another strength of this study was adjusting for multiple covariates that may confound results.

One potential limitation of the Sun et al. (2023) study is the theoretical nature of utilizing an isotemporal substitution approach versus substituting real physical activity in participants. In addition, the data used in this study was strictly observational data making it more difficult to determine causation versus correlation. Lastly, this study was funded by Shanghai Municipal Human Resources and Social Security Bureau, Clinical Research Plan of SHDC, Shanghai Ninth People's Hospital, Innovative research team of high-level local universities in Shanghai, and Shanghai Municipal Health Commission; however, these organizations were not involved in the design or conduction of the study, and they are all government or educational entities.

Cognitive Abilities Improved by Exercise

Abe et al. (2019) conducted a prospective study analyzing the effects of mixed exercise, including yoga, among elderly individuals. Participants were part of a health and welfare center for local community operated by the city government of Okayama prefecture (284), a day service center for an affiliated hospital (84), and a nursing home center for an affiliated hospital (12). Exclusion criteria included past or present central nervous system disease, psychiatric disorders, or medical treatment for dementia. The 385 participants had an average age of 75.5 +/- 8.7 years old. Ethnicity is not specifically stated, but the study was conducted in Japan. There were 75 males and 313 females, no other demographics stated.

The intervention consisted of a 15-minute exercise intervention program developed specifically for this study that consisted of yoga, dry massage, aerobic exercise, and stimulation of pressure points. The study was designed for elderly beginners to exercise. The exercise program was recorded on a DVD and played on a local cable television three times per day. Each group completed the program differently: the individuals at the community center completed the program at least once per week together with instructors with instructions to complete the program at home the other days, individuals at the day center completed the program at least two times per week with instructors with instructions to complete the program at home the other days, and the individuals at the nursing home exercised daily with instructors. The participants were grouped based on the location they were recruited and where they completed the exercise programs (Abe et al., 2019).

Participants were evaluated using a variety of standardized assessments at three time points: baseline, six, and 12 months after exercise therapy intervention. Cognitive assessments included the Mini-Mental State Examination (MMSE), Hasegawa Dementia Score-Revised

(HDS-R), Frontal Assessment Battery (FAB), One-Min Word Recall Screening Tests (letter and category fluency), Clock Drawing Test (CDT), Cube Copying Test (CCT), Trail Making Test (TMT), and Montreal Cognitive Assessment (MoCA). The Geriatric Depression Scale (GDS), Apathy Scale (AS), and Abe's BPSD score (ABS) were used to evaluate depression, apathy, and behavioral/psychological symptoms of dementia. Activities of daily living were assessed using the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Scale. Physical abilities were assessed utilizing grip strength, functional reach test, one leg standing, five-minute walking, and three-minute timed up and go test. MMSE, HDS-R, FAB, ADCS-ADL, FRT, and five-minute walking test were only completed with individuals at the day service center and nursing home. They utilized a one-way factorial analysis of variance (ANOVA) to analyze changes in cognitive, affective, ADL, and physical function assessment scores. *P*-values below 0.05 were considered statistically significant (Abe et al., 2019).

The results were grouped based on the area assessed: cognition, affect, and physical performance. The scores were reported on the various assessments at baseline, six months, and 12 months post initiation of treatment. Mean scores for the cognitive assessments MMSE (0M: 21.7 ± 3.9. 6M: 22.5 ± 4.2. 12M: 23.0 ± 4.2), HDS-R (0M: 21.7 ± 4.9. 6M: 21.8 ± 4.8. 12M 23.0 ± 4.2), and TMT (0.5 ± 0.5, 0.5 ± 0.5, and 0.5 ± 0.5, respectively) scores were relatively stable 6- and 12-months post exercise. Exercise significantly improved FAB scores (0M: 10.7 ± 3.4, 6M: 12.0 ± 3.6, 12M: 13.3 ± 3.6, p -values: 0M vs 12M, $p < .01$, and 6M vs 12M, $p < .05$), CDT (0M: 8.6 ± 1.6, 6M: 9.1 ± 1.3, 12M: 9.7 ± 0.7, p -values: 0M vs 6M and 12M, $p < .01$, and 6M vs 12M, $p < .05$) , CCT (0M: 6.0 ± 1.7, 6M: 6.4 ± 1.2, 12M: 6.7 ± 0.8, p -values: 0M vs 6M, $p < .05$, and 0M vs 12M, $p < .01$) , letter fluency (0M: 7.8 ± 3.0, 6M: 8.1 ± 3.2, 12M: 8.5 ± 3.6, p -values: 0M vs 12M, $p < .01$), and category fluency (0M: 10.1 ± 3.5, 6M: 10.5 ± 3.5, 12M: 11.5 ±

3.7, *p*-values: 0M and 6M vs 12M, $p < .01$). Sub analysis of MMSE scores were performed dividing participants into two subgroups according to baseline MMSE scores (≤ 23 and ≥ 24). The scores in the low baseline (≤ 23) group improved non-significantly. No data reported for the high baseline (≥ 24) group. Sub analysis of HDS-R scores were performed dividing participants into two subgroups according to baseline HDS-R scores (≤ 20 and ≥ 21). The scores were stable during 12 months in the high-baseline group. The scores improved significantly after 12M of exercise intervention in the low-baseline HDS-R, ≤ 20 $p < .05$. Sub analysis of CDT scores was performed dividing participants into two subgroups according to baseline CDT scores (≤ 7 and ≥ 8). The scores in the low CDT group improved significantly: 0M: 6.4 ± 1.0, 6M: 8.3 ± 1.3, 12M: 9.1 ± 1.1. $p < .05$. Sub analysis of CCT scores were performed dividing participants into two subgroups according to baseline CCT scores (≤ 5 and ≥ 6). Scores in the low CCT group improved significantly: 0M: 3.3 ± 1.4, 6M: 5.3 ± 1.4, 12M: 6.1 ± 1.0, $p < .05$. Sub analysis of TMT scores was performed dividing participants into two subgroups according to baseline TMT scores (0 and 1). The scores in the low TMT group improved significantly: 0M: 0.0 ± 0.0, 6M: 0.4 ± 0.5, 12M: 0.7 ± 0.5, $p < .05$ (Abe et al., 2019).

The scores of total GDS, AS, and ABS analyzing affective components were not significantly affected by exercise intervention. Sub analysis for GDS for the higher baseline GDS group (GDS ≥ 5) showed significant improvement at 12M exercise intervention: 0M: 7.9 ± 2.5 vs 12M: 4.8 ± 3.6, $p < .01$. About 30% of the high baseline AS group (AS ≥16) showed significant improvement at 6 and 12M exercise intervention: 0M: 21.3 ± 6.0 vs 6M: 16.7 ± 6.8 and 12M: 15.6 ± 7.1, $p < .01$ (Abe et al., 2019).

The scores from the physical assessments of grasping power of both hands, FRT, and five-minute walk test showed no change at 12M exercise intervention. One-leg standing time increased significantly at 12M exercise intervention: 0M: 28.1 ± 23.6 and 6M: 33.6 ± 23.7 vs 12M: 36.2 ± 23.2, $p < .01$, respectively. The three-minute timed up and go test improved significantly after 12M exercise intervention: 0M: 8.8 ± 5.1 and 6M: 7.9 ± 4.1 vs 12M: 6.9 ± 2.8, $p < .01$ (Abe et al., 2019).

The results revealed that this exercise intervention was effective for maintaining or partially improving cognitive, affective, ADL, and physical functions for a 12-month period in an elderly population. Cognitive scores in FAB, letter and category fluency, CDT, and CCT improved at both 6- and 12-month intervals. This study revealed that this exercise intervention improved BPSD over time, especially in the low-baseline depressive and apathetic groups. In addition, this study revealed improvement in some physical fitness assessments, including one leg standing time and three-minute timed up and go test. This study found that a regular 15-min exercise intervention improved cognitive, affective, ADL, and physical functions on an elderly population. This exercise intervention was notably effective for individuals in the study who were displaying cognitive decline, depressive symptoms, and/or apathy. This intervention also helped maintain functioning in healthy individuals not demonstrating a decline at baseline based on the preintervention scores on the cognitive, affective, and physical assessments (Abe et al., 2019).

Strengths of the Abe et al. (2019) study include the number of participants, length of time, pre and post intervention scores for each participant to control for variability in baseline performance impacting outcomes. In addition, they excluded individuals from the study who had past or present central nervous system disease, psychiatric disorders, or medical treatment for dementia. The population studied is specific to the PICO question. The design of this study being a prospective study and the statistical analysis used are strengths.

There are many potential limitations in this study, particularly with the participants. The study does not discuss any details other than age and sex for the participants. While the baseline assessments describe the function of these individuals for the areas of interest to this study, they do not discuss any health conditions, living environment of the individuals not in the nursing home, or socioeconomic status. There were significantly more participants in the group at the community center. It could be assumed that these individuals may have better overall health due to not needing the extra care provided by a day center or nursing home, but this information is not discussed in the study. In addition, there are significantly more females than males in all groups. This may have exhibited the elderly population as a whole in the area where this study was conducted, but this was not discussed. This was not a blinded study and there was no control group. The study would have been strengthened by comparing the change in scores from the group undergoing intervention and a control group with no exercise intervention. The other big weakness in this study was the variation in how often the exercise intervention was completed amongst the various groups. The individuals at the community center only completed one instructor lead session and the individuals at the day center only completed two instructor lead sessions, whereas the individuals in the nursing home completed five instructor lead sessions. The study did not discuss how they tracked completion of sessions for individuals at home. This was a large flaw in the study and could have explained some of the significant results or lack thereof. To strengthen this study, they should have had all the groups complete the same number of instructor lead sessions. Of course, individual activity level outside of the instructor lead sessions would still vary, but this in addition to a control group, would provide stronger evidence of the specific exercise intervention program leading to the results. It would be interesting to complete the same assessments six and 12 months after the completion of the intervention to see if the results persisted. This study was funded by research grants, but this did not appear to create any bias (Abe et al., 2019).

Huntley et al. (2018) conducted a study to investigate the relationship between known modifiable risk factors for dementia and cognitive function in older adults (> 50 years old). This study is a cross sectional analysis of data taken from the ongoing PROTECT study. The PROTECT study is an online program to study genetics and cognitive function in ageing individuals. The goal of the study is to conduct a 10-year longitudinal study to predict cognitive trajectory and risk by completing annual assessments of cognitive function, lifestyle, and medical history. For this study, researchers used data of individuals who are over the age of 50, live in the UK, comprehend English, and able to use a computer with internet access. Individuals were excluded if they had a diagnosis of dementia. The study enrolled 14,201 individuals with a mean age of 62.06 with a range from 50-101 years. Participants were 71.5% female, 98.3% white, 68.5% married, 48.2% retired, and 84.1% had completed at least A level of education (secondary school plus some college courses).

Individuals who enrolled in the study completed a series of online baseline questionnaires regarding demographic and lifestyle information. This study included information from the questionaries that provided information on education level, smoking, depression, physical activity, perceived social isolation, hypertension, diabetes, and obesity. They also included information on factors they felt may be relevant, including alcohol use, age, diagnosis of heart disease or stroke, marital status, and gender. Participants consented to this study by completing an online registration with information regarding the study (Huntley et al., 2018).

To gather a baseline measure of cognitive function, standardizes assessment were completed using an online cognitive test package consisting of four tasks: The Paired Associate

Learning Task (PAL) to assess visual episodic memory, Self-Ordered-Search (SWM) task assessing spatial memory, Digit Span Task (DS) assessing verbal working memory, and Grammatical Reasoning Task assessing verbal reasoning (VR). Patients were instructed to complete each of these tasks on three occasions during a one-week period to establish a baseline assessment (Huntley et al., 2018).

Statistical analysis was conducted using hierarchical multivariate regression analysis. Each of the four cognitive measures were ran as the dependent variable in separate analyses. Independent variables analyzed were included into the model in a hierarchy based on known risk factors for dementia. For this paper, focus will be on the lifestyle and modifiable risk factors associated with cognitive function. Smoking was significantly associated with a higher score on verbal reasoning ($\beta = 0.421$ (SE 0.144) $p = 0.003$). Smoking was found to have negative effects on paired associates learning and spatial working memory, but these results were not found to be significant. Recent physical exercise was associated with a significantly higher performance on verbal reasoning ($\beta = 1.095$ (SE 0.151) $p < .001$) and digit span ($\beta = 0.130$ (SE 0.025), $p < .001$. Physical exercise had positive effects on PAL and SWM, but these were not found to be statistically significant. Drinking alcohol at least once per week was associated with greater performance on all 4 tasks compared with no alcohol intake (PAL $\beta = 0.074$, $p = .003$; VR $\beta = 1.101$, $p < .001$; DS $\beta = 0.1$, $p = .036$; SWM $\beta = 0.238$, $p = .001$). Drinking alcohol between once a month and once per week was also associated with improved performance on the PAL ($\beta = 0.057$, $p = .046$) and SWM ($\beta = 0.170$, $p = .043$) compared with not drinking alcohol (Huntley et al., 2018).

The results of this study confirm that physical exercise does significantly improve some areas of cognitive function. This study also revealed that smoking and drinking alcohol improves areas of cognitive functioning, despite these being deemed risk factors for dementia (Huntley et al., 2018).

Strengths of this study include the large sample size which allows for greater generalization. The cognitive assessments utilized were all standardized assessments which provides scores that are valid and consistent each time they are administered. The data was analyzed in many ways allowing for multiple conclusions and correlations to be drawn from the study (Huntley et al., 2018).

One limitation of Huntley et al. (2018) study was the lack of definition in lifestyle factors assessed. For example, smoking status was determined by the participants answering the questions, "have you ever smoked?" This leaves room for significant discrepancy in the true effects of smoking status on cognitive functions, since individuals who answered yes to that question could have vastly different smoking histories. In addition, the question regarding physical activity status asked, "Have you done any physical activity lasting at least 20 minutes that has left you out of breath in the last month?" Again, this question is vague and allows for large differences in activity status among individuals who answered yes to this question. The lack of specificity in the questions and answers regarding lifestyle factors makes it difficult to find the data analysis strong enough to contribute differences in cognitive scores to those specific variables. This study also used data from individuals who answered yes to multiple or all questions or potentially no to all or some questions. The study did attempt to account for this variable by checking the assumption of independence of observations using the Durbin-Watson statistic and excluding multicollinearity by inspecting correlation coefficients and Tolerance/VIF values. However, it remains difficult to truly determine if the lifestyle factors individually accounted for the differences in cognitive scores.

APOE4 Carrier Status and Exercise Effects on Risk of Developing Dementia

Vidoni et al. (2022) conducted a non-randomized clinical trial investigating dementia risk and dynamic response to exercise. The study was a single arm, single visit, experimental study with post-hoc assessment of difference in outcomes based on APOE4 carrier status. The study enrolled 62 older adults with a mean age of 75 +/- 5 years with 67% being female and 33% male. Due to inability/refusal to complete the entire study, the sample size for primary outcomes was 59 and 58 for secondary outcomes. Characteristics of participants were self-reported: 89% white, 9.8% Black or African American, 1.6% Asian, 97% sub/urban resident, and 3.3 % rural resident. Participants had an average of 18.8 years of formal education. Participations were given $100 for participating in the study. Exclusion criteria for the study included musculoskeletal or cardiopulmonary restrictions from a physician; contraindications to MRI; anti-coagulant use; previous diagnosis of a cognitive disorder or a neurological or psychiatric condition that could result in cognitive impairment; high exercise risk classification by American College of Sports Medicine criteria, unless cleared by a physician.

The intervention for the study was a 15-minute acute session of moderate intensity exercise on a cycle ergometer. The intensity of the exercise was titrated to 45-55% of the individuals heart rate reserve based on their age-predicted heart rate maximum. Cerebral blood flow (CBF) in cortical gray matter was measured before and immediately post exercise utilizing magnetic resonance imaging (MRI) arterial spin labeling (ASL), defined as the total perfusion (area under the curve (AUC)) following exercise. Following the pre intervention MRI, blood was drawn for APOE4 genotyping, as well as measuring the concentrations of insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and brain derived BNDF. A blood sample was drawn following the post intervention MRI to measure the concentrations of IGF-1, VEGF, and BNDF for pre and post intervention comparison (Vidoni et al., 2022).

The primary outcome for this study was the cortical gray matter cerebral blood flow response to exercise. They also analyzed the change of concentration neurotrophic factor pre and post exercise as an ancillary outcome of interest. The secondary outcomes were changes in blood neurotrophin concentrations of insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and brain derived neurotrophic factor (BDNF). To explore the demographic and intervention differences between APOE4 carriers, the Welch Two Sample test or Fisher's Exact Test were used as appropriate. The primary CBF outcome measure was analyzed utilizing an independent t-test comparison of CBF UAC between APOE4 carrier groups. Secondary outcomes were also analyzed using independent t-tests comparing the change in blood based neurotrophic marker levels, calculating by subtracting the pre-exercise concentration from the post-exercise concentration, and between APOE4 carrier groups. P-values of less than or equal to .05 were considered statistically significant for all analyses (Vidoni et al., 2022).

There was no evidence of an effect of APOE4 carrier status on mean cortical gray matter post-exercise CBF AUC (non-carrier=1,503.6 (259.), APOE4 carrier-1,438.5 (305.9; ($t = 1.3$, $p = 0.19$, 95%CI [-53.9 256.1]). There were not any significant changes in the neurotrophic factors analyzed pre- and post- exercise (change in VEGF and IGF1 $p > .34$, change in BDNF $p = .06$) (Vidoni et al., 2022).

Strengths of this study include the design being prospective, the data analysis methods, as well as the clear explanation of the methods. In addition, the study excluded individuals from the study who had contraindications to participating in neurological imaging and exercise, as well as a diagnosis that may have resulted cognitive impairments. The population studied is specific to the question (Vidoni et al., 2022).

Limitations of this study include the number of participants, non-randomized groups, and lack of information regarding participant characteristics including activity level prior to the study and other comorbid medical conditions that may have impacted the study results. In addition, this study did not explore if the results of this study were repeatable over time or improved any clinical outcomes (Vidoni et al., 2022).

Fenesi et al. (2017) conducted a prospective, population-based study to analyze the relationship between apolipoprotein E (APOE) genotype and exercise on the risk of developing dementia over a five-year period. The study utilized the Canadian Study of Health and Aging (CSHA) dataset to obtain information for individuals to complete the study. Data was gathered from individuals aged ≥ 65 from 36 urban and rural areas located in all 10 Canadian provinces. Initially, a nurse completed an assessment of cognitive function utilizing a Modified Mini Mental State Examination (3MS). Individuals who screened positive on this assessment (3MS < 79) and a random sample of individuals who screened negative (≥ 78) completed a complete clinical assessment by a nurse that included a hearing and vision screen. Following the nurse assessment, a physician completed a neurological examination. In addition, individuals underwent neuropsychological testing if they scored between 50 and 78 on the 3MS. The neuropsychology and physician met to determine a diagnosis for those individuals following testing results. To assess physical exercise and other health-related factors, participants completed a self-reported questionnaire. Individuals were asked, “Do you engage in regular exercise?” to assess physical activity. Follow-up questions about the type and frequency of activity were also asked. Individuals were followed for five years and reevaluated using the methods above and the DSM-

IV criteria for Alzheimer's disease and new criteria for vascular dementia. For individuals who passed away, a relative or other informant provided their cognitive status approximately three months prior to passing. In a subsample of participants, a blood sample was also collected to determine APOE allele status.

Fenesi et al. (2017) analyzed data of 1,646 individuals who provided blood samples for allele status evaluation. To be included in the study, initial cognitive screening had to be negative, or they were never clinically diagnosed with dementia. The control group consisted of the participants who remained dementia free at follow-up testing (n=1,315). The rest of the participants (n = 331) developed some form of dementia: probable Alzheimer's disease (47.7%), possible Alzheimer's disease atypical (9.7%), possible Alzheimer's disease vascular (8.5%), possible Alzheimer's disease Parkinson's (0.01%), possible Alzheimer's disease with co-existing condition (3%), vascular dementia (22.1%), other specified dementia (2.7%), or unclassified dementia (5.7%). In addition to APOE allele status and physical exercise, other factors were analyzed as covariates: sex, age, years of education, prior heart attack, prior stroke, diabetes, high blood pressure, depressing, and smoking.

Results were analyzed utilizing multivariable logistic regression analysis to evaluate if APOE genotype and physical activity predicted dementia risk and if physical exercise status at baseline testing changed the relationship between APOE genotype and dementia diagnosis at follow-up testing. An additional multivariable logistic regression was completed to study the interaction between exercise, APOE genotype, and dementia risk. The regression analysis revealed the odds of developing dementia at follow-up were significantly higher for non-exerciser versus exercises (OR = 1.96, 95% CI = 1.43, 2.67, $p < .001$). The odds of developing dementia were significantly greater for APOE ε4 allele carriers than non-carriers (OR = 2.02, 95% CI = 1.26, 3.23, *p* < .01). There was also a significant interaction between exercise status and APOE genotype (*p* < .01). This relationship was further analyzed based on APOE carrier status. This analysis revealed that for APOE non-carriers, the odds of developing dementia were higher in non-exercisers than exercisers (OR = 1.98, 95% CI = 1.44, 2.71, *p* < .001), but for APOE carriers, the odds of developing dementia were not significantly different between non-exercisers and exercisers (OR = 0.71, 95% CI = 0.46, 1.31, *p* = .34). This study found that exercisers were less likely to develop dementia than non-exercises only if they were not APOE carriers. Since the majority of the population is not at genetic risk, APOE carriers, this study strengthens the need for interventions to prevent dementia to include physical exercise among all older adults (Finesi et al., 2017).

Strengths of this study include a large sample size to generalize results. In addition, the cognitive assessments were completed by trained healthcare professionals with standardized assessments. The data set was pulled from the CSHA that was well developed and robustly studied. The results were analyzed using regression analysis and accounted for covariates that may have impacted results. This is one of the only studies to analyze not only dementia risk and exercise status, but to also include APOE carrier status in as a variable (Fenesi et al., 2017).

Limitations of this study identified by Fenesi et al. (2017) include the utilization of self-reported physical activity via reliable, simple questionnaires and lack of tracking continues physical activity for the duration of the study. Other limitations of this study include lack of demographic information about participants. This study also failed to reveal any additional medical diagnosis that individuals may have developed over the course of the study prior to follow-up. The results of individuals who passed away prior to the five-year period were included with their cognitive status being reported by an individual close to them. This leads to possibility of unreliable dementia diagnosis or missed diagnosis.

Discussion

With the increasing prevalence of dementia, prevention and treatment have been a large focus of research in the medical community. While new treatment options are continually coming to the forefront, effective treatment options continue to be limited making prevention critical. The benefits of exercise in preventing many diseases have been heavily studied. Recently, exercise has been stated to be one of the most important factors in prevention of dementia. This literature review offers supporting evidence for exercise as a key component to reducing the risk of dementia in elderly individuals.

Research has shown that individuals who are physically active are less likely than those who are sedentary to develop dementia. Sun et al. (2023) revealed that increased sedentary time was associated with increased risk of developing dementia. Strengthening that claim, they found replacing sedentary time with physical activity reduced the risk of developing dementia. Interestingly, this study found that the reduced risk of developing dementia was most significant in individuals who were APOE4 carriers. In contrast, a study by Fenesi et al. (2017) found that odds of developing dementia were significantly higher in non-exercisers compared to exercisers in non APOE4 carriers, but this did not hold true for those who were APOE4 carriers. Since it is estimated that 80% of the population are not APOE4 carriers, these results still strengthen the idea of physical activity as a key component in preventing dementia. To further investigate the impact of exercise in dementia prevention in terms of APOE4 status, Vidoni et al. (2022) conducted a study analyzing how exercise impacts cerebrovascular blood flow in the brain, blood based neutrotophic markers, and change in hippocampal size. Because we know that there are specific changes that occur in the brain with dementia, this research helps determine if exercise is an important part of brain health and if it is brain protective from developing dementia. Results of this study found that CBF AUC increased immediately following exercise. It also found no evidence of an effect of APOE4 carrier status on mean cortical gray matter post-exercise cerebral blood flow. In addition, there were not any significant changes in the neurotrophic factors analyzed per- and post- exercise between carrier groups. This indicates that exercise is equally as important for physiological brain health among APOE4 carriers and non APOE4 carriers. It is interesting that Finesi et al. found that exercise did not appear to have the same beneficial effect for APOE4 carriers, but Sun et al. found that the greatest reduction in the risk of developing dementia was in the APOE4 carrier group when exercise replaced sedentary behaviors.

Many research studies have looked at the benefits of exercise in elderly individuals for a multitude of cognitive, physical, functional, and affective components. Because a dementia diagnosis requires a decrease in cognitive, physical, and functional abilities, these studies help strengthen exercise as an important factor to improving and maintaining function to help prevent dementia. A study by Abe et al. (2019) found that exercise was effective at improving cognitive, affective, ADL, and physical functions/abilities in the elderly population. A limitation in the current research on exercise as a preventive measure for dementia is the length of studying the effects of the interventions. Many studies followed individuals for a 6-to-12-month period to look at improvements in specific cognitive areas but did not do any follow-up to see if these improvements ultimately prevented dementia in years to come. A study by Nichols et al. (2022) found that exercise did not improve certain areas of cognition, specifically episodic memory and executive function, in elderly individuals who had subjective cognitive concerns at baseline. It would be interesting to see results of this specific exercise intervention with the same evaluations in individuals without cognitive concerns at baseline. It would also be interesting to look at risk of developing dementia over a longer time frame for the individuals in this study. While this study by Nichols et al. (2022) did not find exercise to improve episodic memory and executive function, studies by Abe et al. (2019) and Huntley et al. (2018) revealed that exercise improves specific cognitive scores in verbal reasoning, FAB, letter and category fluency, CDT, and CCT. In addition, results from the study conducted by Abet et al. (2019) revealed that exercise was specifically effective for individuals who were displaying cognitive decline at baseline.

Overall, exercise has been shown to be an important factor in dementia prevention in elderly adults. In addition, research has shown that longer periods of sedentary behaviors increased the risk of dementia incidence and mortality. The benefits of specific exercise should continue to be studied to offer additional guidance to individuals looking to optimize brain health and prevent dementia. Future research should focus on increased length of studies to analyze if exercise has lasting benefits once stopped and how improved cognitive outcomes in shorter studies correlate to dementia diagnosis later in life.

Conclusion

In conclusion, findings from this literature review support physical exercise as a beneficial strategy to prevent the onset of dementia in elderly individuals. In fact, replacing sedentary behaviors with exercise is one very beneficial way to reduce the risk of developing dementia. Continued research should explore if there is a protective benefit of exercise later in life when exercise was performed regularly earlier in life. Additional research studying the type of exercise and intensity would help individuals know what is the most important to focus on if they are mostly trying to prevent dementia. Follow-up studies analyzing participants dementia status later in life using the same population would be interesting and shed light on how improved cognitive scores with a short course of exercise correlate with the onset of dementia 10 plus years down the road.

Application to Clinical Practice

The importance of regular exercise is stressed to patients by providers for its many benefits, including cardiovascular health and musculoskeletal strength. Current research has shown it is important that providers add the potential for decreasing the onset of dementia with regular physical exercise to the education provided on the importance of physical exercise. In addition, public health resources should add the potential benefit of decreasing onset of dementia with regular physical exercise to educational materials offered to elderly individuals. If patients are known APOE4 carriers, the importance of regular exercise may be even more important to reduce the risk of developing dementia.

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