Article

Association between nonpharmacological interventions and dementia: A retrospective cohort study

Nitya Yerabandi[1*], Shannon Zhu[1*], Tess E.K. Cersonsky[2]
* These authors contributed equally to this work.
[1] Del Norte High School, San Diego, California
[2] Warren Alpert Medical School, Brown University, Providence, Rhode Island

SUMMARY

One of the most common forms of dementia is Alzheimer's Disease (AD), a neurodegenerative disease in which amyloid plaques and neurofibrillary tangles accumulate within the brain, disrupting neuronal function. This commonly results in changes to one's cognition, mood, and behavior. Nonpharmacological interventions, such as cognitive training, physical exercise, reminiscence, music, muscle relaxation, support groups, therapeutic writing, and discussions, have been studied as preventative measures that may delay cognitive impairment in individuals with or without dementia. In this study, we investigated the correlation between physical activity (e.g., sports, recreational activities, traveling), socialization (e.g., family gatherings, clubs/organizations, volunteer work), intellectual stimulation (e.g., occupation, education, reading), and the presence of dementia. We hypothesized that individuals without cognitive impairment would participate in these activities more throughout their lives compared to those with cognitive impairment. This is a retrospective case-control study in which 22 participants from two senior centers in San Diego were interviewed about their lifestyle history. The results of this study showed that there were no statistically significant differences in self-reported activities between individuals with and without dementia. While we intended to measure subject participation in physical, social, and intellectual activities, the results reflected activity recall rather than the activity itself. This points to the need for further research on the deficits in activity recall in individuals with cognitive impairment.

INTRODUCTION

Dementia is a group of progressive neurodegenerative diseases that causes cognitive and physical impairment and severely diminishes a person's quality of life and daily functioning (1-5). More common in older individuals, dementia is accompanied by atypical physical, intellectual, and emotional changes (6). Therefore, the pathological effects of dementia, along with normal age-related declines, can interfere with an individual's ability to live independently and complete daily activities (3, 5, 7). Alzheimer's Disease (AD), the most common type of dementia and the sixth-leading cause of death in the United States, is a progressive

neurodegenerative disease characterized by memory loss, disorientation, difficulty concentrating, and impaired decision-making and problem-solving skills (4, 6, 8-10). These symptoms collectively impair a person's ability to think properly, perform daily tasks, and live a physically and mentally fit life (4). Because pharmacological interventions are limited, investigation of preventative measures for AD is extremely important (5, 6, 8, 11).

Nonpharmacological interventions have gained attention in the field of dementia research as preventative measures that can potentially delay age-related cognitive decline in individuals with and without AD (3). Previous clinical studies on dementia and aging have explored several types of therapeutic exercises and activities, including balance and stretch exercises, memory training, reminiscence therapy, and discussion groups (13, 14). A longitudinal study published in 2020 examined the effect of physical activity on cognition among individuals aged 54 through 75 (n=16,701) from 2004 to 2017 (15). Each participant was asked two questions to gauge the frequency and intensity of their physical activity. To measure changes in cognition, researchers administered one word learning test per participant. Subjects were required to repeat a list of 10 words immediately and then again after 10 minutes to test their immediate and delayed memory. The results showed that engaging in moderate or strenuous physical activity at least once a week positively impacted participants' memories (15). Additionally, one review examined several large cohorts of AD and non-AD (individuals without dementia) subjects and concluded that physical and intellectual activities and socialization have the potential to benefit "cognition and overall well-being," though these hypotheses require further research to clarify to what extent these activities benefit those with AD (13).

RESULTS

To further investigate the impact of physical activity, socialization, and intellectual stimulation on the process of cognitive decline, we conducted a case-control study. Adults with and without a diagnosis of dementia–referred to as AD and non-AD participants respectively– were questioned regarding their previous physical activity, socialization, and intellectual stimulation experiences **(Table 1)**. We also interviewed participants' loved ones, or informants, regarding subjects' lifestyle activities. While several studies in this field

Intervention Type	Activities
Physical Activity	• Sports and recreation • Domestic chores • Journeys lasting several days • Common mode of transportation
Socialization	• Gatherings with family and friends • Involvement in community clubs/organizations • Volunteer work • Caregiving • Local events
Intellectual Stimulation	• Occupation • Education • Number of fluent languages • Reading • Personal creative activities • Technology use • Logical games

Table 1: Types of activities within physical activity, socialization, and intellectual stimulation. Specific items included in the Activity Characteristics Survey for each of the three interventions.

have utilized a longitudinal model, we adopted a retrospective approach in order to determine whether recall would be effective in assessing the benefits of physical activity, socialization, and intellectual stimulation. We hypothesized that these interventions would be more common among individuals without cognitive impairment. Our results showed that across all activities examined, there were no significant differences in the recall of participation between AD and non-AD subjects; we posit that this lack of distinction between the groups may be related to a difference in their retained abilities to recall early activities in one's life.

A total of 22 subjects were enrolled in the study, consisting of 11 AD participants and 11 non-AD participants. Data was collected through a demographic survey and the Activity Characteristics Survey. The baseline age of the 22 participants was 75.3 ± 6.6 years **(Table 2)**. The sample was 90.9% white, 13.6% Hispanic, and 45.5% female. Of the 22 subjects, 7 reported having a family history of neurodegenerative diseases (31.8%).

The baseline age was 77.2 ± 5.9 years in AD participants versus 73.4 ± 7.2 years (p = 0.13) in non-AD participants **(Table 2)**. AD and non-AD subjects were each 90.9% white. Females were overrepresented in the non-AD group (72.7%) relative to the AD group (18.2%). There was no significant difference in activity participation between female and male subjects in both groups. Of the AD participants, 18.2% of them reported having a family history of neurodegenerative diseases compared to 45.5% of the non-AD participants. All AD participants were characterized as having dementia based on their baseline Saint Louis University Mental Status (SLUMS) score of 10.3 ± 3.6 (scores < 21 indicative of dementia) **(Table S2)** (25). All non-AD participants had baseline six-item Cognitive Impairment Test (6-CIT) scores less than 9 points (mean 3.6 ± 3.2), indicative of no cognitive impairment **(Table S2)** (24).

Most subjects in the AD and non-AD groups had difficulty recalling what age they engaged in physical activity, socialization, and intellectual stimulation. To address this, we compared participation in these activities that occurred at any point in the subjects' lives **(Table 3)**. There were no statistically significant differences in activity participation between the AD and non-AD subjects at any point in participants' lives **(Table 3, Table S1)**. These results were consistent across the subjects' and informants' responses. Few comparisons had a p-value of less than 0.05: gender (p = 0.03), medical history

Demographic Characteristic	All Participants (N=22)	Non-AD (N=11)	AD (N=11)	p-Value[1]*
Hispanic/Latino/Spanish Origin	3 (13.6)	1 (9.1)	2 (18.2)	1.00
Race (White)	20 (90.9)	10 (90.9)	10 (90.9)	1.00
Age (years)	75.3 ± 6.6	73.4 ± 7.2	77.2 ± 5.9	0.13
Gender (Female)	10 (45.5)	8 (72.7)	2 (18.2)	0.03
First Language is English	21 (95.5)	11 (100)	10 (90.9)	1.00
Read/Write in English	22 (100)	11 (100)	11 (100)	1.00
Medical History of Neurodegenerative Diseases	11 (50)	0 (0)	11 (100)	<0.001
Family History of Neurodegenerative Diseases	7 (31.8)	5 (45.5)	2 (18.2)	0.36
Chronic Health Condition	5 (45.5)	1 (9.1)	4 (36.4)	0.31

Table 2: Demographic Characteristics of non-AD and AD participants. Race/ethnicity, gender, health history, etc. were collected from non-AD and AD participants. Biological sex and gender were of cis-orientation across all participants. All values are given as mean ± standard deviation (continuous variables) or number (percent) (categorical variables). [1]Non-AD to AD participants. Fisher's Exact Test was used for all variables except for age (Kruskal-Wallis Test).
*p < 0.00556

Activity Characteristic	All Participants	Non-AD	AD	p-Value[1*]
Sports	18 (81.8)	9 (81.8)	9 (81.8)	1.00
Recreational Activities	18 (81.8), N/A = 2	10 (90.9)	8 (72.7), N/A = 2	1.00
Domestic Chores	18 (81.8), N/A = 2	11 (100)	6 (54.6), N/A = 4	0.39
Long Journeys	18 (81.8), N/A = 4	11 (100)	7 (63.6), N/A = 4	1.00
Family Gatherings	20 (90.9), N/A = 1	11 (100)	9 (81.8), N/A = 1	0.48
Clubs, Organizations	14 (63.6), N/A = 7	11 (100)	3 (27.3), N/A = 7	0.27
Volunteer Work	14 (63.6), N/A = 7	10 (90.9)	4 (36.4), N/A = 7	1.00
Attendance at Local Events	17 (77.3), N/A = 3	11 (100)	6 (54.6), N/A = 3	0.16
Caregiving	21 (95.5)	11 (100)	10 (90.9)	1.00
Personality (Introvert)	6 (27.3), N/A = 5	5 (45.5)	1 (9.1), N/A = 5	0.33
Occupation (skilled manual work vs not skilled manual work)	9 (40.9), N/A = 1	4 (36.4)	5 (45.5), N/A = 1	0.67
Education (College)	14 (63.6)	8 (72.7)	6 (54.6)	0.66
Number of Fluent Languages	1.1 ± 0.3	1.3 ± 0.7	1.5 ± 0.7	0.51
Reading	15 (68.2), N/A = 6	11 (100)	4 (36.4), N/A = 6	0.31
Arts, Crafts, and Music	12 (54.6), N/A = 8	9 (81.8)	3 (27.3), N/A = 8	1.00
Item Collections	4 (18.2), N/A = 10	3 (27.3)	1 (9.1), N/A = 10	0.33
Logical Games	18 (81.8)	9 (81.8)	9 (81.8)	1.00

Table 3: Activity Characteristics reported by subjects for Non-AD and AD participants (anytime). Subjects were evaluated for their recalled participation in physical, social, and intellectually-stimulating activities at any time in their life. All values are given as numbers (percentages). Variables with missing values are indicated as non-available (N/A). [1]Non-AD to AD participants. Fisher's Exact Test was used for all variables except number of fluent languages (Kruskal-Wallis Test). *$p < 0.00294$
At least 50% of participants did not have available data for use of non-motorized transportation and technology.

of neurodegenerative diseases ($p < 0.001$), concordance among subject and informant responses for sports ($p = 0.03$), subject-reported participation in reading ($p = 0.10$, marginal), and informant-reported participation in sports ($p = 0.09$, marginal). While the non-AD group appeared to have more years of education, this difference was not statistically significant.

Numerous characteristics were not significantly different between AD and non-AD participants. Demographic similarities were noted, including similar rates of Hispanic ethnicity and white race across both groups **(Table 2)**. Activity participation was similar across all participants for the following variables: sports (anytime and < 20 years of age), family gatherings (anytime), caregiving (anytime), job (60+ years), logical games (anytime), and informant-reported sports (40-60 and 60+ years), recreational activities (anytime), long journeys (anytime), active transportation (20-60+ years), family gatherings (anytime and 60+ years), caregiving (anytime), education, and technology use. Participant and informant reporting was concordant among AD and non-AD participants **(Table 4)**.

DISCUSSION

In this study, we investigated the relationship between different lifestyle activities and the development of AD. Ultimately, we found that, in our sample, there was no relationship between presence of dementia and lifestyle activities, including physical activity, socialization, and intellectual stimulation. Though previous studies have reported an association between dementia and lifestyle history, our findings add to the field of cognitive research by highlighting a similarity in how individuals perceive their life events, even in the setting of severe cognitive decline. Through our interviews of these 22 adults, we observed a diverse range of cognitive function among both the non-AD and AD groups that impacted the recall ability of participants. We learned to adapt our research methods to accommodate these differences in cognition. When interviewing AD participants, we modified the Activity Characteristics survey by incorporating a conversational approach with open-ended questions and visual aids. These adjustments allowed us to minimize stressors to subjects while maximizing recall of past experiences.

Activity Characteristic	All Participants	Non-AD	AD	*p*-Value[1*]
Sports	10 (45.5)	2 (18.2)	8 (72.7)	0.03
Recreational Activities	17 (77.3), N/A = 4	8 (72.7), N/A = 2	9 (81.8), N/A = 2	1.00
Domestic Chores	13 (59.1), N/A = 5	7 (63.6), N/A = 2	6 (54.6), N/A = 3	1.00
Long Journeys	16 (72.7), N/A = 6	9 (81.8), N/A = 2	7 (63.6), N/A = 4	1.00
Family Gatherings	20 (90.9), N/A = 2	10 (90.9), N/A = 1	10 (90.9), N/A = 1	1.00
Volunteer Work	13 (59.1), N/A = 8	9 (81.8), N/A = 1	4 (36.4), N/A = 7	1.00
Attendance at Local Events	11 (50), N/A = 6	7 (63.6), N/A = 3	4 (36.4), N/A = 3	0.28
Caregiving	19 (86.4), N/A = 2	9 (81.8), N/A = 2	10 (90.9)	1.00
Personality (Introvert)	13 (59.1), N/A = 9	7 (63.6), N/A = 4	6 (54.6), N/A = 5	1.00
Occupation (skilled manual work vs. not skilled manual work)	13 (59.1), N/A = 2	7 (63.6), N/A = 2	6 (54.6)	0.37
Education (College)	19 (86.4), N/A = 2	10 (90.9), N/A = 1	9 (81.8), N/A = 1	1.00
Number of Fluent Languages	11 (50), N/A = 8	8 (72.7), N/A = 1	3 (27.3), N/A = 7	1.00
Reading	13 (59.1), N/A = 7	10 (90.9), N/A = 1	3 (27.3), N/A = 6	0.10
Logical Games	15 (68.2), N/A = 2	7 (63.6), N/A = 2	8 (72.7)	1.00

Table 4: Concordance among subjects and informants for Non-AD and AD participants (anytime). Participants were evaluated for consistency in recall of participation in physical, social, and intellectually stimulating activities at any time in their life by confirming with informants. All values are given as count (percentage of responses). Variables with missing values are indicated as non-available (N/A). [1]Non-AD to AD participants, comparison by Fisher's Exact Test. *p < 0.00357. At least 50% of participants did not have available data for use of non-motorized transportation; clubs, organizations; arts, crafts, and music; item collections; and technology use.

Several similarities were found between the characteristics of the AD and non-AD participants. In activity participation, similarities were noted across subject and informant recollection of sports, caregiving, family gatherings, logical games, recreational activities, long journeys, occupation type, education level, active transportation, and technology use. The fairly homogeneous involvement in these activities across AD and non-AD groups demonstrates that participants with AD or dementia did not recall differences in activity, as they reported similar involvement. This reflects known patterns of memory loss in which individuals usually have difficulty with recent recall earlier in the course of the disease but can recall items from their early life or childhood more easily (16-18). Of course, this implies that all individuals in our study were at an early stage of AD, which is unlikely given their level of impairment on SLUMS testing (scores < 21). However, the concordance between informant and subject recall of participants' life activities demonstrates that individuals with and without AD were recalling equally as well. Further studies in this group may elucidate patterns of recall difficulties on these specific items.

Lifestyle changes between AD and non-AD participants may have been subtle enough that they were difficult to identify within a small sample size (n= 22). An analysis of previous clinical studies on nonpharmacological interventions and their impacts on dementia or AD showed that a much larger sample size was required to observe differences in lifestyle between AD and non-AD participants (19, 20). One large (n = 196,383) retrospective cohort study concluded that older adults who had unhealthy lifestyle habits and high genetic predispositions were at a higher risk of developing dementia (19). Another, smaller (n = 551) retrospective study found that, AD and non-AD participants reported a statistically significant difference in the number of activities performed and frequency of intellectual stimulation in early and middle adulthood (20). Therefore, the number of participants included in our study was likely insufficient to detect subtle differences in lifestyle activities across individuals with and without AD or dementia.

Our data collection, as is the nature of a retrospective cohort study, was entirely dependent on whether the participant and informant could accurately recall past activities. Since participants were asked to recall events that extended back into their 20s, participants with and without AD or dementia had difficulty remembering the specific activities that they engaged in throughout their lives. Although we intended to measure participation in lifestyle activities, our results reflected recall abilities of AD and non-AD participants instead. Informants, who were most often children of the participants, were also limited in their ability to provide detailed accounts of their parents' lives. This resulted in

some differences, though insignificant, between subject and informant-reported participation in both groups. Our results suggest that prospective, rather than retrospective studies, may be more effective in identifying the specific interventions most clearly associated with AD. Future studies should consider following a sample over the course of subjects' lifetimes to determine a more accurate record of participation in lifestyle activities.

Performance on cognitive testing is frequently difficult to assess in those with severe cognitive impairment, as many surveys exhibit a floor effect for such participants. To minimize this bias, we assessed activity participation through slightly different methods for each group: our non-AD participants filled out a survey, while our AD participants completed an open-ended interview. This method, designed in concert with the director of a memory care unit trained in such interviews, sought to minimize both the floor effect of a complex survey in a cognitively impaired group and also the emotional stress that such an interview may entail for one with severe impairment. This inherently introduces a source of possible bias in our data, since the two groups did not receive the exact same survey, but the content and our ability to interpret the results was not affected.

As the study was solely conducted in San Diego, California, the demographics of our sample size limited the scope in which our results could be interpreted. With the total sample being predominantly white, the study is not representative of other ethnicities, and the results cannot be generalized beyond this sample. All participants in the control group were members of a community center for active adults that encourages active participation of seniors in programs and recreational activities. Members of this group therefore may not be representative of an average, 60+ individual without AD. Additionally, the gender makeup of both groups was quite different, with eight females in the non-AD group and two females in the AD group. Though numerous studies have suggested that women are at higher risk for dementia or AD, we are not able to make any conclusions on the role of gender as a risk factor (21-23). Several activities were compared between male and female participants; no statistically significant differences were found. Expanding the geographic area of interest and increasing diversity would likely produce results that can be generalized to a larger population.

Our retrospective cohort study found that there was no association between exposure to nonpharmacological interventions and the presence of dementia or AD in our sample. AD and non-AD participants recalled lifestyle details from their personal history at similar levels. We were limited by the small sample size and retrospective design. Future studies can consider a prospective approach with a larger and more diverse sample. Introducing an intervention to a group of participants may enable researchers to better observe the effects of healthy lifestyle habits on the development of dementia or AD.

MATERIALS AND METHODS
Study Design

The AD and non-AD participants were enrolled from two separate senior centers in San Diego, CA; the AD group was recruited specifically from a memory and aging center. Subjects were recruited through the distribution of flyers in-person at each center and via emails sent by the center personnel. All interested individuals or their designated decision-makers contacted the student principal investigators directly. Prospective participants received either a printed or digital copy of an informed consent form with detailed information about the study's purpose, procedure, risks and benefits, information protection methods, and participants' rights and resources. Participants were enrolled in the study after reading and signing the informed consent form; for those without decision-making capacity, as determined by the medical staff of the facility, family members with decision-making capacity gave informed consent.

Inclusion criteria for participation were the following: (1) age 65-80 years, (2) current residence in the San Diego, CA area, (3) non-AD participants were required to not have a medical diagnosis of dementia or AD, and (4) AD participants were required to have a medical diagnosis of dementia or AD. Demographic information, including race, ethnicity, gender, sex, medical history, and family history, was collected using a self-administered survey.

Questionnaires

The 6-CIT was administered to all non-AD participants at the outset of the study to measure baseline cognitive characteristics (11, 20). The brief test includes items such as "What year is it?," "Say the months of the year in reverse," and "Repeat the name and address I asked you to remember" **(Table S2)** (11). The test is scored out of 28 points with a higher score correlating with greater cognitive impairment (11, 24). For each error participants make, points are added to their overall score with each question having a score range varying from 3 to 10. An overall score range of 0-7 is considered normal, 8-9 indicates mild cognitive impairment, and 10-28 indicates significant cognitive impairment (19). This assessment is less sensitive for individuals with dementia and AD and can potentially be emotionally distressing for them. Instead of the 6-CIT, Saint Louis University Mental Status (SLUMS) exam scores for AD participants were provided by the memory and aging center staff **(Table S2)**. Each AD and non-AD participant was identified as having "no cognitive impairment" or "cognitive impairment" based on established cutoffs for 6-CIT and SLUMS (25, 26). Since there is no conversion factor between the two tests, the threshold for cognitive impairment was compared between the 6-CIT and SLUMS exams.

We created an Activity Characteristics Survey **(Table 1)** to obtain data on participant recall of involvement in physical, social, and intellectually stimulating activities throughout an individual's lifetime across several age ranges: 20 to 40 years, 40 to 60 years, and after 60 years of age. Several types

of activities were evaluated for each intervention. These activities were chosen based on validated assessments and existing literature (13, 14, 27, 28). The questions in the survey were open-ended, allowing subjects to state their exact recollections **(Table S3)**. For example, participants were asked "How often did you participate in sports/recreation?" for each age range. The researchers used binary variables ("yes" or "no" responses) to assess whether or not subjects participated in each activity during each age range. To work with people of all cognitive backgrounds, we wanted the opportunity to ask more open-ended questions. AD participants were presented with images to assist them in recalling information relevant to the surveys. Interviews with AD subjects used open-ended questions to facilitate maximum recall and reduce emotional stress for participants with cognitive impairment. Information regarding exposure to lifestyle factors was collected in person or remotely according to appropriate COVID-19 regulations at the time of the interview.

Statistical Analysis

The data for each activity (except for education, occupation, and language) was organized into five variables: activities done in each age range (20-40, 40-60, and above 60 years), activities done at any point in one's life ("anytime" variables), and activities done at an unspecified age. Statistical analyses were performed using Fisher's Exact Test on GraphPad for categorical data. The Kruskal Wallis Test was used for continuous data and conducted on Microsoft Excel. A Bonferroni correction was performed to obtain a modified significance level (**Table 2**: $p < 0.00556$, **Table 3**: $p < 0.00294$, **Table 4**: $p < 0.00357$, **Supplemental Table 1**: $p < 0.00263$).

REFERENCES

1. Breijyeh, Zeinab, and Rafik Karaman. "Comprehensive Review on Alzheimer's Disease: Causes and Treatment." *Molecules,* vol. 25, no. 24, 2020, p. 5789., doi.org/10.3390/molecules25245789.
2. National Collaborating Centre for Mental Health (UK). "Dementia: A NICE-SCIE Guideline on Supporting People With Dementia and Their Careers in Health and Social Care." Leicester (UK): *British Psychological Society* (UK); 2007.
3. Fishman, Ezra. "Risk of Developing Dementia at Older Ages in the United States." *Demography,* vol. 54, no. 5, 2017, pp. 1897–1919., doi.org/10.1007/s13524-017-0598-7.
4. "2020 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia,* vol. 16, no. 3, 2020, pp. 391–460., doi.org/10.1002/alz.12068.
5. Zucchella, Chiara, *et al.* "The Multidisciplinary Approach to Alzheimer's Disease and Dementia. A Narrative Review of Non-Pharmacological Treatment." *Frontiers in Neurology,* vol. 9, 2018, p. 1058., doi.org/10.3389/fneur.2018.01058.
6. Knopman, D. S., and R. C. Petersen. "Mild Cognitive Impairment: A Historical Perspective." *Dementia,* 2010, pp. 395–400., doi.org/10.1201/b13196-57.
7. Haque, Rafi U., and Allan I. Levey. "Alzheimer's Disease: A Clinical Perspective and Future Nonhuman Primate Research Opportunities." *Proceedings of the National Academy of Sciences,* vol. 116, no. 52, 2019, pp. 26224–26229., doi.org/10.1073/pnas.1912954116.
8. "Mild Cognitive Impairment: A Historical Perspective." *Dementia,* 2010, pp. 395–400., doi.org/10.1201/b13196-57.
9. Sahab Uddin, Md., and Ghulam Md. Ashraf. "Introductory Chapter: Alzheimer's Disease—the Most Common Cause of Dementia." *Advances in Dementia Research,* 2019, doi.org/10.5772/intechopen.82196.
10. "Alzheimer's Disease." C*enters for Disease Control and Prevention,* Centers for Disease Control and Prevention, 22 June 2021, www.cdc.gov/dotw/alzheimers/index.html.
11. Abdel-Aziz, K., and A. J. Larner. "Six-Item Cognitive Impairment Test (6CIT): Pragmatic Diagnostic Accuracy Study for Dementia and MCI." *International Psychogeriatrics,* vol. 27, no. 6, 2015, pp. 991–997., doi.org/10.1017/s1041610214002932.
12. Armstrong, Richard A. "The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease." *Folia Neuropathologica,* vol. 47, no. 4, 2009, pp. 289–299.
13. Ruthirakuhan, Myuri, *et al.* "Use of Physical and Intellectual Activities and Socialization in the Management of Cognitive Decline of Aging and in Dementia: A Review." *Journal of Aging Research,* vol. 2012, 2012, pp. 1–14., doi.org/10.1155/2012/384875.
14. Olazarán, Javier, *et al.* "Nonpharmacological Therapies in Alzheimer's Disease: A Systematic Review of Efficacy." *Dementia and Geriatric Cognitive Disorders,* vol. 30, no. 2, 2010, pp. 161–178., doi.org/10.1159/000316119.
15. Lenzen, Sabrina, *et al.* "A Dynamic Microeconomic Analysis of the Impact of Physical Activity on Cognition Among Older People." *Economics & Human Biology,* vol. 39, no. 2, 2020, pp. 12-35., doi.org/10.1016/j.ehb.2020.100933.
16. El Haj, Mohamad, *et al.* "Autobiographical Memory Decline in Alzheimer's Disease, a Theoretical and Clinical Overview." *Aging Research Reviews,* vol. 23, 2015, pp. 183–192., doi.org/10.1016/j.arr.2015.07.001.

17. De Simone, Maria Stefania, *et al.* "Does retrieval frequency account for the pattern of autobiographical memory loss in early Alzheimer's disease patients?" *Neuropsychologia,* vol. 80, no. 1, 2015, p. 199., doi.org/10.1016/j.neuropsychologia.2015.11.024.

18. Dixon, Roger A., *et al.* "Self-reported memory compensation: similar patterns in Alzheimer's disease and very old adult samples." *Journal of Clinical and Experimental Neuropsychology,* vol. 25, no. 3, 2003, pp. 382-390., doi.org/10.1076/jcen.25.3.382.13801.

19. Lourida, Ilianna, *et al.* "Association of Lifestyle and Genetic Risk with Incidence of Dementia." *JAMA,* vol. 322, no. 5, 2019, p. 430., doi.org/10.1001/jama.2019.9879.

20. Friedland, Robert P., *et al.* "Patients with Alzheimer's Disease Have Reduced Activities in Midlife Compared with Healthy Control-Group Members." *Proceedings of the National Academy of Sciences,* vol. 98, no. 6, 2001, pp. 3440–3445., doi.org/10.1073/pnas.061002998.

21. Buckley RF, *et al.* "Sex Differences in the Association of Global Amyloid and Regional Tau Deposition Measured by Positron Emission Tomography in Clinically Normal Older Adults." *JAMA Neurology,* vol. 76, no. 5, 2019, pp. 542-551., doi.org/10.1001/jamaneurol.2018.4693.

22. Letenneur L, *et al.* "Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project." *Journal of Neurology, Neurosurgery, and Psychiatry,* vol. 66, no. 2, pp. 177-183., doi.org/10.1136/jnnp.66.2.177.

23. Beam C. R., *et al.* "Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease." *Journal of Alzheimer's Disease,* vol. 64, no. 4, pp. 1077–1083., doi.org/10.3233/JAD-180141.

24. O'Sullivan, Dawn, *et al.* "Validity and Reliability of the 6-Item Cognitive Impairment Test for Screening Cognitive Impairment: A Review." *Dementia and Geriatric Cognitive Disorders,* vol. 42, no. 1-2, 2016, pp. 42–49., doi.org/10.1159/000448241.

25. Tariq, Syed H., *et al.* "Comparison of the Saint Louis University Mental Status Examination and the Mini-Mental State Examination for Detecting Dementia and Mild Neurocognitive Disorder—a Pilot Study." *The American Journal of Geriatric Psychiatry,* vol. 14, no. 11, 2006, pp. 900–910., doi.org/10.1097/01.jgp.0000221510.33817.86.

26. K. Upadhyaya, Ajaya, *et al.* "The Six Item Cognitive Impairment Test (6-CIT) as a Screening Test for Dementia: Comparison with Mini-Mental State Examination (MMSE)." *Current Aging Science,* vol. 3, no. 2, 2010, pp. 138–142., doi.org/10.2174/1874609811003020138.

27. Nucci, Massimo, *et al.* "Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve." *Aging Clinical and Experimental Research,* vol. 24, no. 3, 2011, pp. 218-226., doi.org/10.3275/7800.

28. Washburn RA, *et al.* "The Physical Activity Scale for the Elderly (PASE): Development and Evaluation." *Journal of Clinical Epidemiology,* vol. 46, no. 2, 1993, pp. 153-162., doi.org/10.1016/0895-4356(93)90053-4.

APPENDIX

APPENDIX

Table S1. Activity Characteristics reported by informants for Non-AD and AD Participants (anytime). Informant-recalled participation in physical, social, and intellectually-stimulating activities at any time in the subject's life. All values are given as numbers (percentages). Variables with missing values are indicated as non-available (N/A). [1]Non-AD to AD participants. Fisher's Exact Test was used for all variables except number of fluent languages (Kruskal-Wallis Test). *$p < 0.00263$

Activity Characteristic	All Participants	Non-AD	AD	*p*-Value[1]*
Sports	11 (50), N/A = 1	3 (27.3), N/A = 1	8 (72.7)	0.09
Recreational Activities	16 (72.7), N/A = 2	7 (63.6), N/A = 2	9 (81.8)	1.00
Domestic Chores	15 (68.2), N/A = 2	8 (72.7), N/A = 2	7 (63.6)	0.32
Long Journeys	19 (86.4), N/A = 2	9 (81.8), N/A = 2	10 (90.9)	1.00
Non-motorized Transportation	0 (0), N/A = 1	0 (0), N/A = 1	0 (0)	1.00
Family Gatherings	20 (90.9), N/A = 1	10 (90.9), N/A = 1	10 (90.9)	1.00
Clubs, Organizations	14 (63.6), NA = 4	8 (72.7), N/A = 2	6 (54.6), N/A = 2	0.58
Volunteer Work	16 (72.7), N/A = 1	9 (81.8), N/A = 1	7 (63.6)	0.31
Attendance at Local Events	16 (72.7), N/A = 3	7 (63.6), N/A = 3	9 (81.8)	1.00
Caregiving	20 (90.9), N/A = 2	9 (81.8), N/A = 2	11 (100)	1.00
Personality (Introvert)	3 (13.6), N/A = 4	2 (18.2), N/A = 4	1 (9.1)	0.53
Occupation (skilled manual work vs. not skilled manual work)	7 (31.8), N/A = 4	1 (9.1), N/A = 4	6 (54.5)	0.15
Education (College)	15 (68.2); N/A = 2	8 (72.7); N/A = 1	7 (63.6)	1.00
Number of Fluent Languages	1.38 ± 0.653	1.3 ± 0.675	1.45 ± 0.688	0.57
Reading	18 (81.8), N/A = 1	10 (90.9), N/A = 1	8 (72.7)	0.59
Arts, Crafts, and Music	10 (45.5), N/A = 3	6 (54.6), N/A = 3	4 (36.4)	0.17
Item Collections	3 (13.6), N/A = 2	0 (0), N/A = 2	3 (27.3)	0.28
Technology Use	20 (90.9), N/A = 1	10 (90.9), N/A = 1	10 (90.9)	1.00
Logical Games	17 (77.3), N/A = 2	9 (81.8), N/A = 2	8 (72.7)	0.22

Table S2. Questions asked in the 6-CIT and SLUMS exams. Questions participants were asked during the administration of the 6-CIT or SLUMS exam (25, 26).

6-CIT (Non-AD participants)	SLUMS (AD participants)
1. What year is it? 2. What month is it? 3. Give the patient an address phrase to remember with 5 components: "John, Smith, 42, High St, Bedford" 4. About what time is it (within 1 hour)? 5. Count backwards from 20-1 6. Say the months of the year in reverse 7. Repeat address phrase: "John, Smith, 42, High St, Bedford"	1. What day of the week is it? 2. What is the year? 3. What state are we in? 4. Please remember these five objects: "apple, pen, tie, house, car." I will ask you again later. 5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20. How much did you spend? How much do you have left? 6. Please name as many animals as you can in one minute. 7. What are the five objects I asked you to remember? 8. Recite these numbers backwards to me: "87, 649, 8537" 9. Put in the hour markers and time at 10 minutes to eleven o'clock. 10. Identify which of the three shapes is the largest and place an "x" in the triangle. 11. Listen to a short story and answer four follow-up questions about it.
0-7 = normal 8-9 = mild cognitive impairment 10-28 = significant cognitive impairment	27-30 = normal 21-26 = mild neurocognitive disorder 1-20 = dementia

Supplemental Table 3. Activity Characteristics Survey Questions. Questions non-AD participants were asked during the administration of the Activity Characteristics Survey.

Intervention Type	Questions
Physical Activity	How often did you participate in sports/recreation?
	How often did you participate in domestic chores?
	How often did you go on journeys lasting several days?
	What was your most frequent mode of transportation?
Socialization	How often did you attend gatherings with loved ones (family, friends, neighbors, etc.)?
	How often did you participate in community clubs or organizations?
	How often did you do volunteer work?
	How often did you attend local events (exhibitions, concerts, conferences, movies, etc.)?
	How often did you participate in caregiving activities (spouses, children, parents, pets, etc.)?
	Please describe your personality. Would you call yourself an introvert, ambivert, or extrovert?
Intellectual Stimulation	What was your occupation? Please list all past occupations you have had.
	How many years of education did you receive?
	How many languages do you speak?
	How often did you read (books, news, magazines, etc.)?
	How often did you engage in personal creative activities (journaling, crafts, item collections, etc.)?
	How often did you use technology (TV, radio, computer, etc.)?
	How often did you play logical games (puzzles, cards, chess, etc.)?