Mental and Physical Activities Delay Cognitive Decline in Older Persons with Dementia


Objectives: To examine the effects of cognitive stimulation (mahjong) and physical exercise (tai chi [TC]) on cognitive performance in persons with dementia.

Design: Cluster-randomized open-label controlled design.

Setting: Nursing homes.

Participants: One hundred ten residents, most of whom were cholinesterase-inhibitor naive. Inclusion criteria were Mini-Mental State Examination (MMSE) = 10–24 and suffering from at least very mild dementia (Clinical Dementia Rating ≥ 0.5). Exclusion criteria were being bedbound, audio/visual impairment, regular activity participation before study, or contraindications for physical or group activities.

Interventions: Homes were randomized into three conditions (mahjong, TC, and simple handicrafts [control]). Activities were conducted three times weekly for 12 weeks.

Measurements: Primary outcome was MMSE. Secondary outcomes were immediate/delayed recall, categorical fluency, and digit span. Various biological risk factors, including apolipoprotein E ε4 allele, were included as covariates.

Measurements were collected at 0 (baseline), 3 (posttreatment), 6, and 9 months.

Results: Intent-to-treat analyses were performed using mixed-effects regression. Mahjong’s effect varied by time for MMSE, delayed recall, and forward digit span. TC had similar effects but not for delayed recall. The typical pattern was that control participants deteriorated while mahjong and TC participants maintained their abilities over time, leading to enlarged treatment effects as time progressed. By 9 months, mahjong and TC differed from control by 4.5 points (95% confidence interval: 2.0–6.9; d = 0.48) and 3.7 points (95% confidence interval: 1.4–6.0; d = 0.40), respectively, on MMSE. No treatment effects were observed for immediate recall and backward digit span.

Conclusions: Mahjong and TC can preserve
functioning or delay decline in certain cognitive domains, even in those with significant cognitive impairment. (Am J Geriatr Psychiatry 2014; 22:63–74)

Key Words: Cognitive decline, dementia, leisure activities, cluster-randomized controlled trial

Longitudinal studies show that leisure activities, especially mental and physical activities, mitigate cognitive decline. Although both physical and mentally stimulating activities are associated with cognitive performance, studies with up to 5 years’ follow-up consistently show that among individuals who were cognitively intact at baseline, only mental activity independently predicts cognitive decline or incident dementia.\(^1\)\(^-\)\(^3\) It is important to note that those who are physically active also tend to be mentally active, and so, the effect of one activity may be masked by the other in survey studies. A recent randomized controlled trial of cognitive training (learning to use the computer), aerobic exercise, and a nil-treatment control did not reveal differences in the cognitive effects of cognitive training and exercise after the 6-month treatment,\(^4\) although the long-term effects were not tested. The therapeutic effects of these activities may be mediated through neuroplasticity,\(^5\)\(^,\)\(^6\) which may attenuate the effects of existing brain pathology, like white matter lesions, on cognitive performance.\(^7\)

Despite encouraging results in healthy older adults, training programs for those with already significant cognitive decline have produced different results. Whereas physical activity has been found to be moderately effective for people with cognitive impairment or dementia,\(^8\) effects of cognitive training on such people have been disappointing.\(^9\) Nevertheless, cognitive training should not be confused with cognitive leisure activities. Cognitive training usually involves tasks tailor-made to tap specific functions, with limited generalizability to untrained domains.\(^10\) These tasks may be unfamiliar and uninteresting to the individual, and participation is difficult for those with low cognitive resources. In contrast, leisure activities are inherently pleasurable and more likely to draw interest and compliance. A recent study showed that active leisure pursuits in the cognitive (e.g., reading and solving crossword puzzles), but not physical, domain in the initial year or so after the diagnosis of Alzheimer disease was associated with a slower cognitive decline, but activities in later years after diagnosis had no effect.\(^11\) However, as with correlational studies, this study could not demonstrate causality and the fact that progressive dementia reduced activity participation in later years\(^11\) made interpretation of the findings difficult. Unfortunately, no experimental study has been conducted on cognitive leisure activities. However, unlike cognitive training, due to the holistic nature of leisure activities, it is difficult to specify exactly which cognitive domains are being trained, and therefore, measures of global cognitive function would be more appropriate outcomes than specific cognitive abilities.

This study tested the effects of two leisure activities, mahjong (a game with 136–152 tiles that is similar to playing cards) and tai chi (TC), against a control in persons with very mild to moderate dementia. An earlier uncontrolled study suggested the efficacy of mahjong in improving the cognitive functions of nursing home residents with dementia,\(^12\) but a randomized controlled trial is necessary for conclusions about causal effects to be made. Moreover, the cognitive effects of TC have never been investigated in individuals with this level of impairment, although a recent randomized controlled trial showed that it helped maintain Clinical Dementia Rating sum-of-box scores up to 1 year over a toning and stretching exercise group in able-bodied older adults with amnestic mild cognitive impairment or very mild dementia only.\(^13\)\(^,\)\(^14\) Thus, this was the first randomized controlled trial investigating the effects of these two activities simultaneously in persons with dementia. Mahjong and TC are popular mental and physical activities, respectively, in Chinese/Asian societies. Most, if not all, persons are well-exposed to these activities, although the degrees to which they master the skills vary. Due to space limitations, shortage of staff, and most importantly, management philosophies that favor maintenance and order but not therapeutic or quality-of-life issues,\(^15\)\(^-\)\(^17\) activity levels of residents in Hong Kong’s nursing homes are typically very low,\(^18\) making it possible to introduce activity programs and
study their effects. We hypothesized that mahjong and TC would lead to enhanced cognitive performance relative to simple handicraft as control.

Intervention effects were assessed after partialing out the effects of a number of potential risk factors, including apolipoprotein E ε4 allele (APOE4; a genetic predisposition for Alzheimer disease), lipids, blood glucose, blood pressure (BP), peak expiratory flow (PEF) rate, depression, chronic illnesses, and demographic factors.

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**METHODS**

**Study Design, Setting, and Participants**

A cluster-randomized open-label controlled trial was conducted. One hundred ten residents recruited from nine nursing homes were randomized by home into three experimental conditions—mahjong, TC, and simple handicrafts (control), with three homes in each condition (Figure 1). Inclusion criteria were Mini-Mental State Examination (MMSE) ≥ 10 or ≤ 24 and less and suffering from at least very mild dementia as indicated by Clinical Dementia Rating 0.5 or more. Exclusion criteria were being bedbound, audio/visual impairment, regular participation in any of the three activities in previous 3 months, or contraindication to participate in exercise or group activities (e.g., arrhythmia, moderate to severe parkinsonism, upper limb paralysis, agitation, and negativism). A cluster design was deemed necessary to avoid treatment contamination within homes. An open-label design was inevitable because activities could not be masked and it was not possible to prevent residents from talking to interviewers about the activities. With four repeated measurements (see below) and time-level intraclass correlation = 0.05, three clusters per treatment condition and n = 10 per cluster were sufficient to detect a small treatment by time interaction effect (Cohen’s d = 0.30) at α = 0.05 and power = 0.80.

Informed consent was obtained from family members, with assent from the participants. Ethics approval was obtained from the Ethics Subcommittee of the Research Committee, City University of Hong Kong, and the Central Research Committee, Hong Kong Institute of Education. The trial was registered with the Chinese Clinical Trial Registry (ChiCTRTRC-09000374).

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**Interventions**

In each condition, participants practiced the activities for 1 hour, three times a week for 12 consecutive weeks. It has been suggested that 2–3 months of cognitive exercise may be the optimal dose. This duration also appeared to be an appropriate dose for TC, judging from previous trials on physical exercise. We adopted the 136-tile version of mahjong, which is the most popular one in Hong Kong. For TC, we used a seated 12-form Yang style that has been tailor-made for frail individuals. For the handicraft group, participants connected beads to create different shapes. This form of group handicraft is appropriate as a control activity because it is less mentally and physically demanding than mahjong and the seated TC but nonetheless provides control for attention and social activity as well as any effects on mood and subject expectancy. All activities were led by an appropriate instructor affiliated with the research team, with assistance from student helpers, for the purpose of standardization. Ratio of student helpers to participants was approximately 1:3 across all groups. (Supplemental Digital Content 1; available online, summarizes other aspects of the intervention protocol.)

**Measures and Procedure**

Primary outcome was MMSE. Secondary outcomes included forward and backward digit sequence as well as digit span, 15-word immediate and 30-minute delayed recall, and categorical verbal fluency (animals, fruits, and vegetables—1 minute per category). Impaired word-list delayed recall (tapping episodic memory) and categorical fluency (semantic memory) are two hallmark features of early-stage Alzheimer disease, although the other cognitive tasks, with the exception of forward digit span/sequence, are also impaired.

The battery of cognitive assessments, together with the 15-item Geriatric Depression Scale, was administered by trained interviewers. Total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose were assessed around 7–8 A.M. on the day of assessment, after 12-hour overnight fasting, by a registered nurse, using calibrated portable devices. BP and PEF (using a peak-flow meter) were taken at the same time. Low-density lipoprotein cholesterol was estimated using the Friedewald formula.
genotyping was done by restriction fragment length polymorphism approach according to a modified method. In this sample, there was only one person who was APOE4-homozygous, and so, all participants who carried the APOE4 allele were lumped into a group (0 = no APOE4, 1 = with APOE4). In addition, home staff provided information on cholinesterase inhibitor use (0 = none, 1 = yes) and diagnosed coronary heart disease, stroke, hypertension, diabetes, and chronic obstructive pulmonary disease, all of which have been implicated in cognitive decline. A composite score (0–5) indicates the number of illnesses diagnosed in the participant. All outcome measures and covariates, except APOE4 and medical diagnoses, were obtained at baseline and subsequently at 3 (posttreatment), 6, and 9 months.

Moreover, residents were free to participate in activities. It was possible that they participated in activities intended for another treatment group (e.g., a control participant playing mahjong in his or her leisure time) as well as in other activities of a similar nature (e.g., TC might not be the only physical activity). Hence, we asked nursing home staff to record on a daily log sheet their participation in
various leisure activities (not limited to mahjong, TC, and handicrafts) throughout the entire study period; up to three activities lasting 20 minutes or more were recorded daily. During the 12-week intervention period, only activities that were not assigned for the trial were recorded. Finally, new falls and strokes after the start of the intervention were recorded on a weekly sheet.

**Statistical Analysis**

Analysis of variance and $\chi^2$ tests were conducted to examine whether the groups differed at baseline on the outcome measures as well as potential confounding factors. For the main analyses, there were three levels in the data structure: repeated measurements (level 1), within participants (level 2), and within homes (level 3). Home-level intraclass correlations for all outcome measures were 0.00–0.02 (mean = 0.01). Intent-to-treat analyses were performed on the multilevel data structure with mixed-effects regression, using full-information maximum likelihood estimation in Stata version 11.1 (StataCorp, College Station, Texas). The advantage of this procedure is that the missing data imputation is not necessary because the conditional distribution of missing data on the basis of the observed data is incorporated into the estimation of the parameters. Therefore, data available from all the participants were included to provide unbiased estimates.39 In the regression models, the intercepts and effects of time were specified to vary randomly at home and participant levels, whereas the regression coefficients of the predictors were treated as fixed effects. Within-person covariance over time was specified using an unstructured model. All regressions were linear models aside from those for immediate and delayed word-list recall, for which Poisson modeling for discrete events was used as the words correctly recalled were few.40 Measures were entered as time-varying predictors when they were obtained at all time points. (Supplemental Digital Content 2; available online, provides a detailed explanation of the multilevel equations.)

There were one primary outcome and seven secondary outcome measures in this study, and hence, a risk of Type I error inflation for the secondary outcomes. The Bonferroni correction is overly conservative when the number of tests is high, the sample size is small, and the outcome measures are correlated.41 Not surprisingly, the present set of secondary outcome measures was moderately correlated across all time points (average $r = 0.33$). Following the recommendation by Bender and Lange,41 we treated the analyses involving secondary outcomes in an exploratory fashion and did not adjust the p value. This is appropriate, given the novelty of this type of research. Thus, for all tests, $\alpha$ levels were set at 0.05 (two-tailed).

We performed a number of procedures to select appropriate variables for the final analytical model. First, we tested to see whether the effects of intervention varied by time and APOE4 status. The latter was included because of the potency of APOE4 on cognitive decline19 and because of the increasing need to understand factors that moderate the effectiveness of psychosocial interventions for older people.42 As there were three groups, two dummies were created, with the control as the reference group, and product terms were created between the two treatment groups on the one hand and time (centered) and APOE4 on the other. These product terms were included to examine whether treatment effects varied by time and APOE status. Only time showed moderating effects, and product terms involving APOE were dropped. Second, we explored the effects of other covariates, including age, sex, education, chronic illnesses, BP, lipids, glucose, PEF, depression, cholinesterase inhibitor use (time-varying), and new falls (no participant experienced stroke during the study period). Bivariate correlations showed that age, sex, cholinesterase inhibitors, and new falls were unrelated to outcome variables and were dropped. Low-density lipoprotein cholesterol correlated at $r \sim 0.87$ across all time points with total cholesterol, and so, it was dropped to avoid collinearity. We then regressed each outcome measure on the remaining covariates, together with APOE4. Only education, APOE4, chronic illnesses, PEF, and depression had independent effects on the outcomes. Finally, we recomputed the findings, using a final model consisting of mahjong, TC, time, mahjong × time, TC × time, education, APOE4, chronic illnesses, diastolic BP, PEF, and depression (the last three were entered as time-varying predictors). Diastolic BP was also included as a covariate as there was a group difference at baseline.

When interactions between groups and time were significant, we probed at which time point treatment effect occurred by calculating the adjusted mean
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difference between treatment and control. As mahjong and TC were coded as dummies, this was done by calculating the simple slopes at specific time points. For linear regression, effect size was indicated by Cohen’s d. For Poisson regression, effect size is the exponential function of the simple slope\(^43\); the difference from 1 represents percentage change in the outcome measure due to treatment as compared with control.

Finally, two supplementary analyses were performed. First, as mentioned earlier, participants might initiate activities prescribed for another experimental condition, thus contaminating estimates of treatment effects. We repeated the analyses for the subsample without such crossover activities throughout the 9-month period; two control, three mahjong, and four TC participants were excluded accordingly. Because the sample size became smaller, we reduced the number of covariates by including only those that were significant in the main analyses. (We did not report detailed data on activity participation after the intervention because the frequencies were low and had no impact on the outcomes beyond that of the experimental assignment; see also another report\(^18\).) Second, as indicated previously, the treatment groups were coded as dummies with control as the reference group; thus, mahjong and TC were each compared with control but not with each other. To ascertain whether the effects of mahjong and TC were significantly different from each other, we dropped the control group while recoding TC = 0 and mahjong = 1, thus allowing direct comparison between the latter two.

RESULTs

The three groups did not differ on any baseline characteristic other than diastolic BP (Table 1), which was included as a covariate in further analyses. Mixed-effects regression (Table 2) showed a significant negative effect of time on MMSE and digit forward memory (both span and sequence), meaning that these cognitive abilities declined with time. People with APOE4 had lower verbal memory (word-list recall) and MMSE. Higher education was associated with better digit forward memory but not in delayed recall and categorical fluency for which the relationships were surprisingly reversed. PEF appeared to be a good biological marker for cognitive decline, with low PEF being consistently associated with lower MMSE, categorical fluency, and digit forward memory, although its relationship with delayed recall was surprisingly reversed. Depression and diastolic BP were also associated with selected measures.

Mahjong’s effect varied by time for MMSE and forward digit span and sequence. It also had main effects on these measures as well as on categorical fluency. TC had the same interactions with time, but no main effects on any variables. The mahjong/TC-by-time interaction effects are displayed in Figure 2. These interaction effects were driven by a gradual decline in the performance of control participants, whereas the performances of the mahjong and TC groups were maintained or even improved, so that the differences between treatment and control were enlarged over time. In fact, significant difference between groups usually appeared at 6 and 9 months only, when control participants had reached a certain degree of decline. This pattern was rather robust, as when a measure did not show prospective decline (i.e. effect of time was nonsignificant or positive; Table 2), the treatment by time interaction did not exist. By 6 and 9 months, the primary outcome measure of MMSE showed a difference between mahjong and control equal to 3.0 (95% CI: 0.9—5.0; d = 0.34) and 4.5 (95% CI: 2.0—6.9; d = 0.48) points, respectively, and a difference between TC and control equal to 2.3 (95% CI: 0.4—4.2; d = 0.26) and 3.7 (95% CI: 1.4—6.0; d = 0.40) points, respectively. In addition, over the 9-month period of the study, the control group dropped 2.9 points (95% CI: −4.2 to −1.7) on the MMSE, whereas the mahjong group and the TC group gained 1.5 (95% CI: −0.0 to 3.0) and 1.3 (95% CI: −0.0 to 2.5) points, respectively.

For the secondary outcomes, at 6 and 9 months, mahjong differed from control by (a) 1.11 (95% CI: 0.45—1.77; d = 0.31) and 1.78 (95% CI: 0.86—2.71; d = 0.45) points, respectively, on forward digit span, and (b) 1.02 (95% CI: 0.33—1.70; d = 0.27) and 1.68 (95% CI: 0.78—2.57; d = 0.42) points, respectively, on forward digit sequence. By comparison, TC differed significantly from control at 9 months only (difference between means: 0.98; 95% CI: 0.12—1.84; d = 0.25) on the forward digit span measure. Despite the overall significant interaction with time on forward digit sequence, the individual means were not significantly different from those of the control group at all time points.

For categorical fluency, only a main effect by mahjong (overall mean: 13.4, SD: 12.4; 95% CI: 9.3—17.5) over
control (overall mean: 9.9, SD: 12.7; 95% CI: 5.7–14.2) was observed. No effects for mahjong and TC were observed for verbal memory (whether immediate or delayed recall) and digit backward memory.

**Supplementary Analysis**

The first supplementary analysis by dropping participants with crossover activities produced essentially the same results. The second analysis comparing mahjong against TC showed a significant mahjong main effect for categorical fluency (Z = 2.11, p = 0.034) and forward digit span (Z = 2.06, p = 0.039), as well as a significant mahjong-by-time interaction effect for forward digit sequence (Z = 1.96, p = 0.050). However, there was no significant difference between the two treatments on the primary outcome MMSE. On the whole, there was some evidence that mahjong might be better than TC in preserving selected cognitive domains.

**DISCUSSION**

This study provided experimental support to the effects of mental and physical activities in delaying...
<table>
<thead>
<tr>
<th></th>
<th>MMSE B (95% CI)</th>
<th>Verbal Immediate Recall B (95% CI)</th>
<th>Verbal Delayed Recall B (95% CI)</th>
<th>Categorical Fluency B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahjong</td>
<td>2.240 (0.361 to 4.118)</td>
<td>0.019</td>
<td>0.311 (0.026 to 0.648)</td>
<td>0.071</td>
</tr>
<tr>
<td>Tai chi</td>
<td>1.617 (-0.175 to 3.410)</td>
<td>0.077</td>
<td>0.076 (-0.247 to 0.399)</td>
<td>0.646</td>
</tr>
<tr>
<td>Time (centered)</td>
<td>-0.978 (-1.395 to -0.564)</td>
<td>&lt;0.001</td>
<td>0.095 (-0.035 to 0.224)</td>
<td>0.152</td>
</tr>
<tr>
<td>Mahjong x time</td>
<td>1.477 (0.829 to 2.124)</td>
<td>&lt;0.001</td>
<td>0.127 (-0.076 to 0.330)</td>
<td>0.219</td>
</tr>
<tr>
<td>Tai chi x time</td>
<td>1.395 (0.818 to 1.972)</td>
<td>&lt;0.001</td>
<td>0.095 (-0.088 to 0.277)</td>
<td>0.309</td>
</tr>
<tr>
<td>Education</td>
<td>-0.745 (-1.629 to 0.143)</td>
<td>0.100</td>
<td>-0.131 (-0.309 to 0.048)</td>
<td>0.152</td>
</tr>
<tr>
<td>APOE4</td>
<td>-1.904 (-3.467 to -0.342)</td>
<td>0.017</td>
<td>-0.337 (-0.655 to -0.021)</td>
<td>0.036</td>
</tr>
<tr>
<td>Chronic illnesses</td>
<td>-0.135 (-0.724 to 0.459)</td>
<td>0.661</td>
<td>-0.134 (-0.253 to -0.015)</td>
<td>0.027</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.001 (-0.024 to 0.021)</td>
<td>0.900</td>
<td>0.002 (-0.005 to 0.009)</td>
<td>0.563</td>
</tr>
<tr>
<td>PEF</td>
<td>0.007 (0.005 to 0.012)</td>
<td>0.001</td>
<td>0.001 (-0.000 to 0.002)</td>
<td>0.058</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.058 (-0.158 to 0.042)</td>
<td>0.256</td>
<td>-0.013 (-0.041 to 0.014)</td>
<td>0.341</td>
</tr>
</tbody>
</table>

**Notes:** p values were based on Z tests; those <0.05 are boldfaced.
FIGURE 2. Effects of treatment varied with time on [A] MMSE, [B] forward digit span, and [C] forward digit sequence. Scores displayed are means adjusted for education, APOE4, chronic illnesses, diastolic blood pressure, peak expiratory flow, and depression. Error bars denote 95% confidence intervals. Bars with letters a, b, and c indicate significant difference from control group based on Z tests; *p < 0.05, **p < 0.01, ***p < 0.001.
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cognitive decline in individuals with dementia and extended a recent study that showed that mahjong, but not TC, had short-term effects on reducing depressive symptoms in nursing home residents with dementia.\textsuperscript{18} The findings are important because, although similar studies have been done on physical activity,\textsuperscript{8} this study represented the first randomized controlled trial on cognitive leisure activity in individuals with dementia, with a built-in activity-control group and repeated assessments of cognitive performance up to 9 months or 6 months after the completion of treatment. Results supported the relatively long-term benefits of both types of activities, although there was preliminary evidence that mahjong might be more effective than TC in short-term memory of numerical units. The relative superiority of mahjong in short-term digit memory could not be attributed to practice effects as all the three groups were exposed to the same amount of practice over time.

Not all mental activities are equally effective. It appears that only cognitively demanding activities (e.g., mahjong), or what some researchers call “complex” cognitive activity,\textsuperscript{4,7} may benefit individuals for whom decline is already under way, whereas less-demanding activities (e.g., simple handicrafts) may not do the same. Moreover, although TC tended to have smaller effects than mahjong, our analysis showed that they were not very different from each other. The findings paralleled that of a recent study showing that a computer course and a physical exercise program produced similar improvements in episodic memory and executive control over a nil-treatment control group in healthy older women.\textsuperscript{4} However, it should also be noted that TC is different from most other physical exercises in that it requires memorization of complex motor sequence and may hence have additional benefits on memory when compared with other forms of physical exercise without such an element.\textsuperscript{13} To what extent the present findings about TC can be generalized to other exercise modalities in this population remains to be researched.

Not all cognitive domains benefited from TC and mahjong. As expected, there were positive effects on global cognition (i.e., MMSE). Consistent with a preliminary study,\textsuperscript{12} digit forward, but not digit backward, memory benefited. No effects on verbal memory were found. Moreover, mahjong had a main effect but no interaction with time on categorical fluency. Judging from the baseline scores and regression results favoring digit forward memory over other cognitive tasks (aside from MMSE), it appears that the strongest effects of leisure activities are in domains (in this case, short-term memory) that are relatively well-preserved to begin with. (No normative data on digit span exist for very old populations, but a study involving 118 Chinese older adults age 72.8 years and without dementia reported a mean forward digit span of 7.4 units.\textsuperscript{31}) More research incorporating other cognitive measures is needed to test the limits of such interventions.

Study Limitations

We acknowledge three limitations in this study. First, a major limitation was the lack of blinding, as activities could not be masked and it was not possible to prevent residents from talking to interviewers about the activities. Nevertheless, interviewers were blind to the hypothesis and all outcome measures were objective tests. Second, participants were recruited after randomization, leading to a possible selection bias, which is a common issue in cluster designs. However, this is the only way to prevent treatment contamination in nursing home settings. Moreover, the groups did not differ on a large number of potential confounds other than diastolic BP, which was controlled in subsequent analysis. Finally, as is true in this region, few participants were on cholinesterase inhibitors. Thus, it is not clear whether the results are specific to older adults with dementia who are cholinesterase-inhibitor naive. Future studies are needed to investigate whether these psychosocial treatments would add to the effects of medications to produce optimal treatment effects.\textsuperscript{42} Despite these limitations, it is noteworthy that all homes were committed to implementing the condition to which they were assigned, with few attritions over time. The longitudinal design, together with a randomized control group in a population with high risk for cognitive decline, provides strong support for the therapeutic effects of selected leisure activities in old age, even in those with significant cognitive impairment. Although we do not yet have data about how such activities work in conjunction with medications, the fact that they can lead to significant improvements in MMSE is an important

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support for their therapeutic values, especially in developing countries where prescriptions for cholinesterase inhibitors may be deterred by costs. For the nursing home population in particular, policies and practices that provide active support for leisure activities of sufficient intensity are warranted in light of the present findings.

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Author contributions: STC is the principal investigator and led study design, data analysis, and writing the article. PKC and STC designed the study protocol and managed the project together; in addition, PKC designed certain instruments, collected data, and contributed to the writing. YQS performed APOE genotyping and contributed to the writing. JHML assisted STC in data analysis and writing of the results. ECSY and TMCL contributed to the initial study design and to the training of research assistants for administering certain assessment instruments. ECSY and ACMC assisted in the recruitment of study settings.

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