Combined physical exercise-working memory training on slowing down cognitive decline in elders with mild clinical Alzheimer disease: a randomised controlled study (abridged secondary publication)

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KEY MESSAGES

1. A total of 376 participants with mild dementia were randomly assigned to four 6-week programmes: (1) working memory training, (2) physical exercise, (3) combined working memory and physical exercise, or (4) health education, with 94 participants per group.
2. Immediately after training, all groups showed a time effect for better clinician-rated global cognition function (measured by Clinical Dementia Rating Sum of Boxes), episodic memory, and category verbal fluency. There was no significant between-group difference in cognitive outcomes.
3. The cognitive performance tended to deteriorate after intervention stopped. Adherence to training is important for sustainable benefits. More intensive schedule and longer duration of practice should be advised for sustained benefits.

Hong Kong Med J 2022;28(Suppl 3):S28-30
HMRF project number: 12133801

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Introduction

In Hong Kong, over 10% of the population aged ≥70 years have clinical dementia.[1] There is an urgent need for developing adjuvant interventions to attenuate cognitive decline in people with dementia. Working memory (WM) training has been reported to improve cognitive function.[2] Higher levels of participation in physical exercise (PE) modulate cognitive decline and delay clinical impairments in dementia.[3]

The present study aims to determine whether PE augments the benefits of WM training in people with early-stage dementia. We evaluated the cognitive benefits of a 6-week twice weekly programme of combined PE and WM training over PE alone or WM training alone. We also evaluated the logistics of a structured training protocol as an adjuvant intervention for people with clinical dementia.

Methods

This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. The study protocol has been registered at the CCT Clinical Trials Registry of the Chinese University of Hong Kong (ChiCTR-IOR-15005942).

A total of 376 participants aged 60 to 90 years were recruited through social centres for elders in Hong Kong. Inclusion criteria were a diagnosis of major neurocognitive disorder secondary to Alzheimer disease, having Clinical Dementia Rating score of 1 indicating mild dementia, and being ambulatory with low risk of fall. Exclusion criteria were a past history of bipolar affective disorder or psychosis, physical frailty affecting attendance to training sessions, already attending regular cognitive training, a history of major neurological deficit (stroke and traumatic brain injury), and major communicative impairments. Participants were not enrolled in other structured cognitive or exercise training during the study period.

Participants were randomly assigned to four groups: (1) the WM training group (20 minutes of WM training, followed by 5 minutes of rest, and another 20 minutes of WM training), (2) the PE group (20 minutes of PE, followed by 5 minutes of rest, and another 20 minutes of PE), (3) the PE-WM group (20 minutes of PE, followed by 5 minutes of rest, and then 20 minutes of WM training), and (4) the health education (control) group (45 minutes of

health education interactive talks with a 5-minute break in between). There were 12 sessions in 6 weeks (twice weekly); each session lasted 45 minutes.

Participants were assessed at baseline, week 6 (intervention phase), and week 12 (monitoring phase). Primary outcome measure was the Chinese version of the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog).[4] Secondary outcome measures were Clinical Dementia Rating sum of boxes (CDR-SOB), specific cognitive tests comprising episodic and working memory, attention, language, and executive function, the Chinese version of the Neuropsychiatric Inventory, the Disability Assessment for Dementia, and the Quality of Life – Alzheimer Disease.

Results

A total of 376 participants (301 women and 75 men) were equally randomised into the WM, PE, PE-WM, and control groups for intention-to-treat analyses. The mean age of participants was 80.4±6.5 years, and the mean years of education was 3.2±3.8 years. As for global cognitive function, the mean Mini-Mental State Examination score was 21.2±2.9, and the mean ADAS-Cog score was 16.5±5.8. The mean number of items in 10-minute learning delay recall was 2±2.3 out of 10. There were no significant group differences in baseline demographic, cognitive, or functional profile (Table 1).

At week 6 (intervention phase), the four groups demonstrated improvements in global cognitive function as measured by CDR-SOB (P=0.01, Table 2), but not in the ADAS-Cog score. The WM-PE group showed greater (but not significantly) improvement than other groups. In addition, the four groups demonstrated improvements in category verbal fluency test (P=0.01) and delayed recall (P=0.01). Delayed recall improved more (but not significantly) in the WM-PE group.

At week 12 (monitoring phase), there was no significant change in ADAS-Cog score. CDR-SOB

TABLE 1. Demographic and cognitive profiles of participants at baseline

Characteristic	Working memory training (n=94)*	Physical exercise (n=94)*	Working memory training & physical exercise (n=94)*	Control (n=94)*	ANOVA / Chi square	P value
Age, y	79.8±6.4	80.3±6.2	80.7±7.0	80.8±6.3	0.49	0.687
No. of men : women	19:75	16:78	18:76	22:72	1.25	0.741
Education, y	3.7±3.9	2.5±3.6	3.4±3.8	3.3±3.9	1.64	0.179
Clinical Dementia Rating sum of boxes	3.6±1.2	3.6±1.2	3.5±1.2	3.6±1.2	0.08	0.970
Mini-Mental State Examination	21.3±2.7	21.1±3.0	21.4±2.9	21.1±2.9	0.34	0.793
Alzheimer's Disease Assessment Scale – Cognitive Subscale	15.9±5.9	16.7±5.8	16.5±6.0	17.0±5.7	0.51	0.672
Delay recall	2.1±2.3	1.9±2.2	2.1±2.5	1.8±2.3	0.39	0.761
Category verbal fluency test	29.2±8.8	28.1±9.4	28.6±8.5	28.1±8.6	0.33	0.805

* Data are presented as mean ± standard deviation

TABLE 2. Change in cognitive profiles from baseline to week 6 after adjusting for attendance

Cognitive outcome	Working memory training (n=94)*		Physical exercise (n=94)*		Working memory training & physical exercise (n=94)*		Control (n=94)*		Linear mixed-effects model
	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	Baseline	Week 6	
Clinical Dementia Rating sum of boxes	3.6±1.2	3.2±1.5	3.6±1.2	3.2±1.5	3.5±1.2	3.1±1.5	3.6±1.2	3.3±1.6	Time effect, P=0.01
Alzheimer's Disease Assessment Scale – Cognitive Subscale	15.9±5.9	16.3±6.8	16.7±5.8	16.2±7.1	16.5±6.0	15.7±6.7	17.0±5.7	16.9±6.4	-
Delay recall	2.1±2.3	2.6±2.7	1.9±2.2	2.4±2.5	2.1±2.5	2.8±2.7	1.8±2.3	2.5±2.5	Time effect, P=0.01
Category verbal fluency test	29.2±8.8	31.2±11.3	28.1±9.4	29.7±10.2	28.6±8.5	30.3±9.2	28.1±8.6	29.6±9.2	Time effect, P=0.01
Digit span - backward	2.3±1.2	2.4±1.3	2.0±1.2	2.2±1.0	2.3±1.2	2.3±1.2	2.1±1.1	2.2±1.1	-
Visual span - backward	2.0±1.4	2.3±1.1	2.0±1.3	2.2±0.8	1.9±1.3	2.3±1.0	2.1±1.1	2.3±0.9	-

* Data are presented as mean ± standard deviation

score did not show any time or group effect. In addition, improvement in backward visual spans was observed (P=0.05). However, episodic memory deteriorated in all four groups (P<0.001).

From baseline to week 12, the ADAS-Cog score did not change significantly. From baseline to week 6, the four groups demonstrated improvements in global cognitive function as measured by CDR-SOB (P<0.01). There were no group differences in the changes of ADAS-Cog and CDR-SOB scores. From baseline to week 6, backward visual spans improved across time (P=0.01), with no significant group differences. Episodic memory was stable in all groups. Category verbal fluency test improved in all groups (P<0.001), with no significant group differences.

There was no significant change in scores of the Neuropsychiatric Inventory, the Disability Assessment for Dementia, and the Quality of Life – Alzheimer Disease across time from baseline to week 12.

Discussion

After the 6-week training programme, all groups showed improvement in clinician-rated global cognition function (measured by CDR-SOB) but not in ADAS-Cog. There was also improvement in cognitive test scores (delayed recall of list learning, category verbal fluency, and backward visual spans). There was no significant group difference in terms of outcome.

During the monitoring phase, most groups showed a decline in global cognition function as measured by ADAS-Cog. In participants with >70% attendance (completers), the programme was associated with stabilisation of ADAS-Cog and episodic memory scores, as well as improvements in global cognition, verbal fluency, and working memory scores, although practice effects could not be excluded. Nonetheless, we observed no significant change in quality of life, mood, behavioural symptoms, and daily functioning.

Regarding sustainability of cognitive benefits, only the WM group showed improvement in global cognition function after 6 weeks. The absence of similar improvement in the WM-PE group may infer that a dose effect is important. Further studies may consider exploring intervention programmes with higher duration, intensity, and frequency.

The intervention programme did not lead to an improvement in everyday functioning. This may infer that longer-term intervention, or specifically designed functional enhancement programmes, should be tested for its potential efficacy in maintenance of function in people with dementia.

Conclusion

The 6-week training programme was associated with improvements in global cognitive function, verbal fluency, and episodic memory, but sustainability of benefits was very limited beyond intervention periods.

Acknowledgements

We thank the participants and their family members, as well as the elderly social centres for generous help and enthusiasm. We also thank our research staff Ada Fung, Ken Lai, Matthew Lo, Vivian Lai, Lisa Ma, Yan Law, and Harriet Tang for their help.

Funding

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#12133801). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

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