Topic: Effect of physical exercise and medication on enhancing cognitive function in older adults with vascular risks

* Ada Wai-Tung FUNG [1]

[1] Department of Applied Social Sciences, The Polytechnic University of Hong Kong, Hong Kong SAR, China.

*Corresponding Author:
Ada, Wai Tung, Fung
EF710, 7/F, Core E, Department of Applied Social Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong SAR, China
Tel: 1-852-2766-5744
Fax: 1-852-2773-6558
E-mail: awt.fung@polyu.edu.hk
ORCID: 0000-0001-7439-3503

Word count: 2525 words

Contributors

AWT Fung involved in the study design, data collection, statistical analysis and interpretation, writing and editing of manuscript.

Abstract

Aims: To examine the association of physical exercise (PE) and medication on cognitive function in older adults with vascular risks.

Methods: This was a cross sectional study on 478 non-demented participants aged 60 years and above with vascular risks. Management strategy included PE (mind-body exercise and/or strenuous exercise), medication, PE in combined with medication, and no management at all. Participation of PE was determined by self-reporting exercise engagement in the past year. Cognitive preservation was defined as a global composite z-score that was equal to or above the age and educational adjusted mean of cognitively normal older adults. Binary logistic regression was performed to examine the association between management strategy and cognitive preservation in each exercise modality adjusted by sociodemographic, physical, mental and genetic factors.

Results: Association was found in preserved cognitive function for those who managed their vascular risks through PE (OR= 2.5, 95% CI 1.2 – 5.3, p= 0.015) and in combined with medication (OR=2.1, 95% CI 1.0 – 4.6, p=0.05). A similar pattern was also found in each exercise sub-type. A significant short term (OR=3.6, 95% CI 1.0 – 12.4, p=0.042) to lifelong (OR=3.5, 95% CI 1.4 – 8.5, p=0.006) cognitive benefit was found in MB exercise.

Conclusion: Medication alone may be insufficient to preserve cognitive function in older adults with vascular risk. In our sample, medication in combined with PE is found to have significant impact on cognitive improvement. MB exercise may be better than strenuous exercise, as a more sustainable cognitive effect is observed.

Keywords: Cognitive preservation, lifestyle advice, exercise habit, vascular care, active ageing.

Introduction

Multiple vascular risks, such as hyperlipidemia, hypertension and diabetes are common among older adults[1]. Vascular risks account for much of the mortality, disability, functional decline, hospitalization, and healthcare costs in the older population worldwide [2], and are associated with an increased risk for developing cerebrovascular insults and stroke. They are also established risk factors for elevated risk of cognitive decline, and incidence of Alzheimer's disease (AD) and vascular dementia (VaD) [3].

Unfortunately, evidence on the use of cardiovascular treatment, such as statin, on improving both cardiovascular diseases (CVDs) and cognitive outcome in older adults with vascular risks is still under much debate due to uncertainty of medication use relating to efficacy and safety in older adults, especially for those aged 75 or older [4, 5]. Previous cohort studies and randomized controlled trials (RCTs) on the cognitive effect of statin use in older adults showed mixed results due to poorly defined cognitive profiling and the use of non-standardized methods to detect cognitive impairments [6, 7]. Similarly, clinical trial data has failed to find clear cognitive benefits in aggressively treated hypertensive older adults due to short trial duration [8]. The high residual vascular risks in intensively treated older adults suggested the presence of other risk factors in life that are not fully managed by medication alone [9].

With a higher proportion of physical inactivity, cigarette smoking and unhealthy diet, it is not surprising to see an increasing trend of CVDs and related risks in developed countries. Enormous studies suggested that physical exercise (PE) might be beneficial to the cognitive function in healthy older adults through enhancement of cardiovascular fitness, cerebral circulation and neuroplasticity [10-12]. However, it is not known if the cognitive effect of PE will add on or facilitate medication to provide further protection to community dwelling older adults with vascular risks.

It is of interests to investigate the association of PE and medication on cognitive function based on the current situation on the self-management strategy among this specific population. Furthermore, we would explore on the association of different exercise modalities on the preservation of cognitive function in older adults with high vascular risks. We postulated that PE in combined with medication would have a superior cognitive effect than either treatment alone. Our study might provide convincing demonstration on the beneficial effect of combining primary and secondary levels of vascular care in the community, and ultimately help to promote and encourage PE in older adults with high vascular risks to prevent cognitive decline.

Methods

Study design and participants

This was a cross-sectional study on a sample of 478 non-demented community dwelling older adults with vascular risks and aged 60 years or above. The sample was drawn from a larger pool of 613 older adults who took part in a community survey on cognitive health [(13)]. Individuals with a clinical dementia rating (CDR) of 0.5 or above and psychotic disorders were excluded from the analysis. All participants were interviewed between 2012 and 2013 and underwent an extensive list of assessments on lifestyle activities pattern, physical and mental health statuses, cognitive functioning, biological markers and sociodemographic information. Informed consent was obtained before the interview. The study was approved by ethics committee of the Chinese University of Hong Kong.

Measurements

Vascular risks

Vascular risks were defined as the presence of any of the following criterion: (1) hypertension was defined by self-report of a clinical diagnosis; or a measurement of a systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg; or on antihypertensive medication. (2) diabetes mellitus was defined by self-report of a clinical diagnosis; or having a fasting plasma glucose level of ≥ 7 mmol/L; or on blood glucose lowering medication; (3) hyperlipidaemia was defined by self-report of a clinical diagnosis; or having a total cholesterol level of > 8 mmol/L or low-density lipoprotein (LDL) level of < 4.9 mmol/L, or on lipid lowering medication; (4) obesity was defined as a having a Body Mass Index (BMI) of > 30 kg/m^2; (5) smoking status was characterized as never, quitted or current smoking with number of cigarettes smoking per day; (6) Excessive alcohol consumption was defined as 4 alcoholic drinks for women and 5 or more for men in a single occasion for 5 or more days in the past month; and (7) physical inactivity was defined as having less than 30 minutes of physical exercises three times per week. A summary vascular risk score was also calculated by assigning 1 point for each of the above conditions. The score ranges from 0-7, with higher score indicating greater level of vascular risks.

Management strategy

Management strategy referred to the method being used by older adults to modify their vascular risks. Based on the use of medications and/or physical exercise, vascular management were categorized into four types: (1) physical exercise; (2) medication; (3) physical exercise in combined with medication; and (4) no management at all.

Physical exercise (PE)

PE was evaluated with a self-report questionnaire on lifestyle activity participation. Older adults who reported of engaging in any kind of PE during the past 12 months were classified as "Exercise" group. PE was further divided into mind body (MB) exercise and strenuous exercise. MB exercise encompasses Six forms, Tai chi, Qi gong, Pak duen kam, and yoga, whereas strenuous exercise includes moderate to strong intensity activities, such as running, hiking, swimming, ball games, and etc. Level of participation was evaluated based on number, frequency (daily, several times a week, weekly, several times a month, monthly, bimonthly and 3 months or longer), and duration during the past 12 months. They were also asked to indicate the total number of years of practice [(14)].

Primary outcomes

Global cognitive functioning

CDR was utilized to diagnose severity of clinical dementia [(15)]. Cantonese version of the mini-mental state examination (CMMSE) was used to assess global cognition [(16)]. The score ranges from 0 to 30 with a general cut-off point of 19/20, indicating possibility of suffering from dementia. Other cognitive performance was measured by category verbal fluency test (CVFT) [(17)], and 10-minutes delayed recall extracting from the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) [(18)]. A composite score on global cognitive functioning was calculated based on the sum of three z-scores that are converted from the raw scores of CMMSE, CVFT and delayed recall.

Potential confounding variables

Socio-demographic information include age, years of education, gender (male/ female) were obtained. Physical burden was evaluated using the Cumulative Illness Rating Scale (CIRS) [(19)]. Mental health status was assessed using the Revised Clinical Interview Schedule (CIS-R) that diagnosis of common mental disorders, according to the Tenth Revision of the International Classification of Diseases of the World Health Organization (ICD-10) diagnostic criteria [(20)]. Genotyping was grouped based on the presence of apolipoprotein e4 (ApoE4), so participants with one or more copies were categorized as e4 carrier.

Statistical Analyses

In this study, older adults with CDR 0 and a vascular risk score of 1 or above were included in the analysis. Cognitive functioning was categorized into: (i) poor cognitive functioning if the global composite cognitive score exceed one standard deviation (SD) below the age and educational adjusted mean of older adults with CDR 0; and (ii) preserved cognitive functioning if the global composite cognitive score was equal to or above the adjusted mean. Binary logistic regression analyses were performed to investigate which management strategy and PE would be associated with preserved cognitive function. Potentially confounding variables included in the binary logistic regression were age, gender, education, physical comorbidity, mental health problems, and genotyping. Data analysis was performed using IBM SPSS 23.0 for Windows. Statistical significance was set at a level of 0.05.

Results

Management strategy in older adults with vascular risks

The sample (N=478) has a mean age of 68.6 years (SD=6.3) with a mean year of education of 9.9 years (SD=4.7). More than half (54.6%) were females. Close to one-third (28%) of the sample engaged in some forms of PE to manage their vascular risks. About a quarter (23.6%) of the sample relied on medication only to modify their vascular risks. Slightly more than one third (32.8%) of the sample adopted exercise in combined with medication to manage their vascular risks. The remaining 15.5% had never exercised nor took any medication to manage their vascular risks. Table 1 shows the management strategy that endorsed by older adults with vascular risks during the past 12 months.

We have also compared the demographic variables and physical illness burdens for MB exercise and strenuous exercise between individuals being excluded for stopping exercise with those who remained in the analysis. For MB exercise, we found that individuals being excluded have significantly more physical illness burdens than those who remained in the analysis ($t=-3.650$, $p<.001$). For strenuous exercise, likewise, those being excluded have significantly more physical burdens than those who remained in the analysis ($t=2.804$, $p=.006$).

Cognitive effect of different exercise modality

After adjustment on sociodemographic factors, physical burdens, mental health status and APoE4 genotype, we found an increased odd in preserved cognitive function in those who managed their vascular conditions through only PE (OR=2.5, 95% CI 1.2 – 5.3, p=0.015) and in combined with medication (OR=2.1, 95% CI 1.0 – 4.6, p=0.05). However, no association with the use of medication was found in the sample.

Similar pattern was also observed in each exercise subtype. Binary logistic regression has shown an increased odd in preserved cognitive function in those who endorsed

MB exercise in combined with medication (OR= 2.9, 95% CI 1.1 – 7.7, p= 0.029) and strenuous exercise in combined with medication (OR= 2.4, 95% CI 1.1 – 5.3, p= 0.036). Table 2 displays the associations (in odd ratio and 95% confidence interval) between management strategy and preserved cognitive function in terms of different exercise modalities.

Short- and long-term cognitive effects

Further analysis was performed to investigate association between years of practicing different exercises and preserved cognitive function. After controlling for sociodemographic factors, physical burdens, mental health status and APoE4 genotype, a higher odd for preserved cognitive function was found in those who practiced MB exercise for 1-5 years (OR=3.6, 95% CI 1.0 – 12.4, p=0.042), 6-10 years (OR= 3.2, 95% CI 1.2 – 8.6, p=0.023), and over 11 years (OR=3.5, 95% CI 1.4 – 8.5, p=0.006). For strenuous exercise, only those with a practice of 1-5 years was associated with an increased odd of preserved cognitive function (OR=2.3, 95% CI 1.0 – 5.1, p=0.046). Table 3 shows the odd ratio of preserved cognitive functioning in older adults with vascular risk on different types of exercise by years of practice.

Discussion

The study evaluated the cognitive effect of various management strategies in a community sample of older adults with vascular risks. Our findings demonstrated that physical exercise or in combined with medication was associated with preserved cognitive function in our sample. While most studies reported the beneficial effect of physical exercise on cognitive function in both healthy and cognitively impaired older individuals, our study has extended the current evidence to older adults with vascular risks [(21)].

Although association was found between physical exercise and preservation of cognitive function, the relationship appeared to be weak. An explanation might be the inclusion of older individuals who were not particularly fond of exercise or tended to exercise irregularly. The problem of heterogeneity in exercise frequency and intensity often identified in observational studies [(22)]. However, our findings suggested that any forms of spontaneous exercise in the neighborhood without coaching might also provide cognitive benefit to older adults with vascular risks. It could encourage the at-risk group with a rather passive management strategy, such as taking medication only or keeping basic daily chores, to take on an exercise habit even in a minimal amount to reduce sedentariness and other lifestyle risks for neuroprotective effects on structural and functional brain changes [(21)].

In this study, more than half (56.4%) of the participants were on some type of vascular medications. While therapeutic medication may have direct clinical basis to reduce vascular risks, there appeared no association in providing cognitive benefits. This finding is important because it suggested that the risk of developing cognitive impairments could not simply be amenable to pharmacological vascular treatment. Our interpretation has gained some supported from previous studies on the insufficiency in reliance on medication to enhance cognitive function in older adults at risk of developing cognitive impairment (23). In clinical practice, vascular conditions are commonly treated with multiple drugs, but treatment target are not always reached as intended in the older population. It could be mostly due to polypharmacy and drug interaction effect that affected drug tolerance and compliance in this group.

Contrary to our hypothesis, cognitive function in the physical exercise in combined with medication group was not better than but comparable to exercise group. An explanation might be that the biological mechanisms, such as neurogenesis, underlying cognitive effect of physical exercise are lacking in drug treatment (24). Animal studies further confirmed the mediating role of brain-derived neurotrophic factors (BDNF) between physical exercise and hippocampal neurogenesis (25). In addition, physical exercise and vascular medication are targeting different vascular conditions that associate in the ageing process. Previous studies showed that regular physical exercise might serve to improve arterial stiffness, peripheral vascular function and cerebral circulations, whereas the goal of drug treatment mainly aimed at symptoms control and prevention of worsening of already existing conditions (26). It is possible that physical exercise exerts its cognitive effect by improving vascular and brain health simultaneously, and such effect is not related to medication use.

While the above findings agreed on the cognitive effect of physical exercise, a more relevant question to ask might be on the type and duration of physical exercise to be suggested for older adults with vascular risks. This study has comprehensively provided information on the short-term, intermediate and long-term effect on MB and strenuous exercises in older adults at high risk of developing cognitive impairment. Our findings showed a differential exercise-induced cognitive effect between MB and strenuous exercises. More specifically, an initial cognitive effect was found in short-term engagement of strenuous exercise. This might be due to the increasing difficulty in sustaining the required intensity of motor activity in strenuous exercise as individuals aged. Animal studies have already demonstrated the association in intense motor activity and cognitive effect in neurogenesis and brain molecular changes in rodents [27]. On the contrary, a significant and continuous prolonged cognitive effect was found in older adults who engaged in MB exercise. This is consistent with a recent meta-analysis of the relationship between MB exercise and better cognitive performance across different domains [28]. Most importantly, our finding showed that the cognitive effect of MB exercise could enhance with increasing lifelong exposure, suggesting that brain plasticity is possible in older people in response to the dual stimulations of MB exercise.

This study has several strengths. First, we included older adults with a wide range of modifiable vascular risk factors that could add on together to influence subsequence CVD and cognitive outcomes. It might help to extrapolate our findings to intensively treated older adults whose risk of developing cognitive decline might be amenable to simple lifestyle modification, such physical exercise. This would help to avoid the use of ineffective or excessive treatments in older adults with vascular risks. Put it differently, our result supported the use of primary care as an assistive therapy to secondary care in older adults with vascular risks for dementia risk reduction. Therefore, our result might have influence on the current clinical practice and some effects on reducing burden on the healthcare system in the long run.

Second, we have carefully inspected the cognitive effect in older adults with varying exercise patterns. As suggested by the use it or lose it theory, cognitive function could be maintained or improved through continuous brain stimulation. Individuals who stopped exercise were excluded from the analysis, as reduction of activity level might likely to reflect physiological deterioration or onset of other illnesses that could potentially affect the cognition for a prolonged period. We also avoided the possibility of any carry-over effects of previous physical exercise practice on cognition.

Furthermore, our findings revealed the endorsement of poor vascular management among older adults with vascular risks in Hong Kong. Close to 40% of our sample led a sedentary lifestyle or chose to rely on therapeutic medications only to manage their vascular conditions. This information reflects the attitude of older adults towards medical help seeking and possibly a misunderstanding that therapeutic medication alone is good enough to manage the conditions. Older adults on vascular medications might not be aware of the need to commit both physical exercise with medication to obtain the full benefit of cognitive effect. To effectively prevent cognitive impairment in older adults with vascular risks, the role of regular exercise plus optimal symptom control should be emphasized. Currently, only a small portion of older adults enjoys the cognitive benefits that brought by the combined management strategy. The phenomenon found in this study, if continue, would have poor implication on cognitive decline and incidence of dementia in the long run. Therefore, our study has provided us with updated data on the behavioral preference of older adults and revealed the need to promote the benefits of physical exercise in combined with medication to those following a passive vascular management strategy.

Several limitations were noted in this study. First, we did not have data on how long each vascular risk has been developed. The effect on cognitive function would be more profound and diverse in older people with mid-life vascular risks. Second, this was a cross-sectional study. We could not examine the reverse causation of vascular risks on cognitive function in our sample. Some studies found that low blood pressure or sudden weigh loss in late life could be associated with cognitive decline (29, 30).

Our findings demonstrated a clear benefit combining primary and secondary levels of vascular care for better cognitive outcome in the community. Medication alone may be insufficient to enhance cognitive functioning in older adults with vascular risks. Commitment is needed in both physical exercises and medication to obtain additional cognitive benefits. MB exercise provides a more sustainable cognitive benefit than does strenuous exercise to older adults with vascular risks. Our study provides useful information for health centers to structure a continued care for older adults with high vascular risk to prevent cognitive decline. It also helps to promote active lifestyle in conjunction with medication in those at risk of cognitive decline due to vascular risks.

Acknowledgments
This study was supported by the Lui Che Woo Institute of Innovative Medicine (Project Code: 8303102).

Conflicts of interest
The authors declare no conflict of interest.

References

1. Peters SAE, Wang X, Lam TH, Kim HC, Ho S, Ninomiya T, et al. Clustering of risk factors and the risk of incident cardiovascular disease in Asian and Caucasian populations: results from the Asia Pacific Cohort Studies Collaboration. BMJ Open. 2018;8(3):e019335.
2. World Health Organization. Prevention of cardiovascular disease. Guidelines for assessment and management of cardiovascular risk. 2007 [Available from: http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf.
3. Kapasi A, Schneider JA. Vascular contributions to cognitive impairment, clinical

Alzheimer's disease, and dementia in older persons. Biochim Biophys Acta. 2016;1862(5):878-86.

4. Armitage J, Baigent C, Barnes E, Betteridge DJ, Blackwell L, Blazing M, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. The Lancet. 2019;393(10170):407-15.

5. Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. Vasc Health Risk Manag. 2010;6:775-85.

6. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, et al. Statins and Cognitive Function. Annals of Internal Medicine. 2013;159(10):688-97.

7. Rojas-Fernandez C, Cameron J-C. Is Statin-Associated Cognitive Impairment Clinically Relevant? A Narrative Review and Clinical Recommendations. The Annals of pharmacotherapy. 2012;46:549-57.

8. Wright Clinton B. Should Hypertension Be Treated in Late Life to Preserve Cognitive Function? Hypertension. 2018;71(5):781-6.

9. Alagiakrishnan K, McCracken P, Feldman H. Treating vascular risk factors and maintaining vascular health: is this the way towards successful cognitive ageing and preventing cognitive decline? Postgraduate medical journal. 2006;82(964):101-5.

10. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;14(2):125-30.

11. Hotting K, Roder B. Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev. 2013;37(9 Pt B):2243-57.

12. Niemann C, Godde B, Staudinger UM, Voelcker-Rehage C. Exercise-induced changes in basal ganglia volume and cognition in older adults. Neuroscience. 2014;281:147-63.

13. Fung AWT, Lam LCW. A cross-sectional study on clinical correlates of anxiety disorders in 613 community living older adults in Hong Kong. Int J Geriatr Psychiatry. 2017;32(7):742-9.

14. Leung GT, Leung KF, Lam LC. Classification of late-life leisure activities among elderly Chinese in Hong Kong. East Asian archives of psychiatry : official journal of the Hong Kong College of Psychiatrists = Dong Ya jing shen ke xue zhi : Xianggang jing shen ke yi xue yuan qi kan. 2011;21(3):123-7.

15. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr. 1997;9 Suppl 1:173-6; discussion 7-8.

16. Chiu HF, Lee, H. C., Chung, W. S., Kwong, P. K. . Reliability and validity of the Cantonese version of the Mini-Mental State Examination — a preliminary study. .

Journal of Hong Kong College of Psychiatry. 1994;4(SP2):25-8.
17. Chiu HF, Chan CK, Lam LC, Ng KO, Li SW, Wong M, et al. The modified Fuld Verbal Fluency Test: a validation study in Hong Kong. J Gerontol B Psychol Sci Soc Sci. 1997;52(5):P247-50.
18. Chu LW, Chiu KC, Hui SL, Yu GK, Tsui WJ, Lee PW. The reliability and validity of the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) among the elderly Chinese in Hong Kong. Annals of the Academy of Medicine, Singapore. 2000;29(4):474-85.
19. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc. 1995;43(2):130-7.
20. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychol Med. 1992;22(2):465-86.
21. Tyndall AV, Clark CM, Anderson TJ, Hogan DB, Hill MD, Longman RS, et al. Protective Effects of Exercise on Cognition and Brain Health in Older Adults. Exercise and Sport Sciences Reviews. 2018;46(4).
22. Schott N, Krull K. Stability of Lifestyle Behavior – The Answer to Successful Cognitive Aging? A Comparison of Nuns, Monks, Master Athletes and Non-active Older Adults. 2019;10(1347).
23. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373(9667):929-40.
24. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A. 2007;104(13):5638-43.
25. Liu PZ, Nusslock R. Exercise-Mediated Neurogenesis in the Hippocampus via BDNF. 2018;12(52).
26. Barnes JN, Corkery AT. Exercise Improves Vascular Function, but does this Translate to the Brain? Brain Plast. 2018;4(1):65-79.
27. Ehninger D, Kempermann G. Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. Cereb Cortex. 2003;13(8):845-51.
28. Zhang Y, Li C, Zou L, Liu X, Song W. The Effects of Mind-Body Exercise on Cognitive Performance in Elderly: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2018;15(12).
29. Power MC, Weuve J, Gagne JJ, McQueen MB, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. Epidemiology. 2011;22(5):646-59.

30. Suemoto CK, Gilsanz P, Mayeda ER, Glymour MM. Body mass index and cognitive function: the potential for reverse causation. International Journal of Obesity. 2015;39(9):1383-9.