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Cognitive Benefit of a Multidomain Intervention for Older Adults at Risk of Cognitive Decline: A Cluster-Randomized Controlled Trial

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ABSTRACT

Objective: *We sought to assess cognitive benefits of a community-based multidomain intervention for improving cognition among older adults at risk of cognitive decline (COMBAT).* ***Design:*** *A two-armed cluster-randomized controlled trial.* ***Setting and Participants:*** *Community-dwelling older adults aged 60 years or older and were at risk of cognitive decline (n = 209).* ***Intervention:*** *In this 9-month intervention study, 10 community hospitals in Beijing, China, were randomized (1:1) to receive either a multidomain intervention of meditation, cognitive training, exercise, and nutrition counseling or usual care. The intervention was delivered with weekly 1-hour group training sessions and weekly home homework.* ***Measurements:*** *Primary outcome was change in cognition as measured by a composite Z score of seven cognitive tests. Secondary outcomes included subjective cognitive abilities, positive and negative affective experiences, physical activity, and dietary habits. Assessments were administered at baseline, end of the intervention, and 1 year after completing the intervention (1-year follow-up).* ***Results:*** *Immediately after the intervention, the intervention group showed significant enhancement in cognitive performance (p = 0.026). The between-group difference in the Z score of change of cognition was 0.20 (95% CI: 0.053, 0.35), with a Hedges'* g *of 0.40 (95% CI: 0.29, 0.50). However, this cognitive benefit was not significant at*

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1-year follow-up. ***Conclusion:*** *This multidomain intervention was effective to improve cognition for at-risk individuals. Long-term effects on cognitive function and individual differences in response to the intervention deserve further investigation.* (Am J Geriatr Psychiatry 2023; 31:197−209)

HIGHLIGHTS

- **What is the primary question addressed by this study?**
  We investigated the effects of a 9-month community-based multidomain intervention of mindfulness meditation, cognitive training, exercise, and nutrition counseling on improving cognition compared to controls for Chinese older adults having risks of cognitive decline.
- **What is the main finding of this study?**
  Multidomain intervention had immediate benefits on improving cognitive performance measured by objective assessments and subjective cognitive abilities relative to the control, and the benefits on subjective cognitive abilities were retained for 1 year after the completion of the intervention.
- **What is the meaning of the finding?**
  Multidomain intervention that targeted multiple predictors of cognitive decline can have immediate benefits on improving cognitive performance for older adults at risk of cognitive decline. Long-term effects on cognition and individual differences in response to the intervention deserve further investigation.

OBJECTIVE

China has the largest population of patients with cognitive impairment, and the prevalence of dementia and mild cognitive impairment has been increasing over the last few decades.[1] Since there is currently no effective cure, great efforts have been made to identify preventive measures to maintain cognitive functions. Recent studies suggested that about 35%−55% of dementia cases, especially in low- and middle-income countries, are theoretically preventable through elimination of potentially modifiable risk factors.[2] Several factors have been identified as predictors for cognitive declines, such as low educational attainment, hypertension, obesity, diabetes, physical inactivity, smoking, depression, and social isolation.[2] This provides a great potential for implementing preventive intervention to reduce risk of cognitive decline.

Due to the multifactorial nature of cognitive impairment, a few multidomain intervention studies that targeted several modifiable risk factors simultaneously have been completed in Europe,[3−6] and several ongoing trials worldwide are being planned as well.[7] Those studies showed mixed results on the effectiveness of multidomain intervention on improving cognition or reducing the incidents of dementia. For instance, the FINGER trial in Finland showed that after a 2-year intervention in cognition, exercise, diet, and vascular risk monitoring, at-risk individuals had more improvement in cognitive performance relative to a care-as-usual control group.[6] Some small-scale trials also found supporting evidence for a positive effect,[8−10] but two large-scale intervention studies in the Netherlands and France failed to find an overall effect.[4,5] Although more trials are needed to prove the efficacy, emerging evidence supports the potential of multidomain intervention to prevent dementia or slow down cognitive decline. Of note, similar intervention studies are currently not available in China.

Inspired by the FINGER trial, we developed a cluster-randomized trial of community-based multidomain intervention for improving cognition among at-risk older adults (COMBAT) in Beijing, China. We targeted older adults aged 60 years or older from communities, with risk factors associated with cognitive decline identified in the literature.[2,11,12] We made several adaptations to the intervention program. Specifically, we incorporated a mindfulness meditation training component because it can reduce negative emotions like depression, which has been shown to link to cognitive decline.[13,14] However, no multidomain intervention studies have ever included emotion management as one training module.[3] In fact, a randomized controlled trial found that learning emotion regulation strategies before cognitive training can significantly reduce levels of anxiety for community-dwelling older adults with subjective memory complaints.[15] Therefore, adding the mindfulness meditation component could potentially benefit at-risk individuals. In addition, the intervention training was delivered with two components, weekly group sessions led by instructors and at-home self-monitoring completed as homework. Previous studies have suggested that adherence decreased with increased intensity of intervention programs,[16] which might hurt the efficacy. Thus, the combined delivery method may lower the difficulty for older adults to attend in-person training, such as time commitment and participation effort, while keeping the intensity of practice at a relatively frequent pace by doing self-monitoring homework.

Therefore, the COMBAT study was a cluster-randomized controlled trial of a community-based multidomain intervention of mindfulness meditation, cognitive training, physical exercise, and nutrition counseling, aiming to improve cognitive function for community-dwelling older adults having risks of cognitive decline.

METHODS

Study Design and Participants

The COMBAT study was a cluster-randomized controlled trial among community-dwelling residents in Beijing, China. The study protocol was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Sciences, Beijing, China. All participants gave written informed consent at screening and baseline visits. The trial was registered at Chinese Clinical Trial Registry (www.chictr.org.cn), number ChiCTR1900025487. The reporting follows the guidelines of the CONSORT extension for cluster randomized trials.[17]

Community regional hospitals (the cluster units) were recruited through a partnership with the Beijing Chaoyang District Center for Disease Control and Prevention. Eligible hospitals were required to have at least 5,000 older adults registered and available places for conducting the intervention. Among 41 available hospitals, 10 hospitals were eligible and finally enrolled, and there was no geographical overlapping in the communities they served.

The intervention targeted at-risk older adults, that is, those who only showed slight or no impairment in cognitive performance but had identified risk factors for cognitive decline.[3,11,12] Screening assessment was conducted in person at community hospitals, including a neuropsychological battery, self-report of medical history, and taking a blood sample to test for *APOE* $\varepsilon 4$ genotypes. Inclusion criteria were (1) age older than 60 years; (2) having subjective cognitive complaints as indicated by the self-rated Ascertain Dementia 8-Item Questionnaire (AD-8) score greater than or equal to 2;[18] (3) possessing at least 2 of the listed well-recognized risk factors:[2,11,12] educational level below primary school, physical inactivity, depressive symptoms as indicated by Center for Epidemiologic Studies Depression Scale (CES-D) score greater than or equal to 16,[19] smoking, or having hypertension, diabetes, heart disease, or cerebral infarction; and (4) having risks of cognitive decline as indicated by either carrying *APOE* $\varepsilon 4$ allele, the Mini-Mental State Examination (MMSE) score greater than or equal to 26,[20] or Paired Associative Learning Test (PALT) score greater than or equal to 6.5 ($Mean_{Screening\text{-}Sample} - 0.2$ SD).[21] Exclusion criteria were previously diagnosed dementia; substantially poor cognitive performance (MMSE score < 18); severe depressive symptoms (CES-D score of > 28); and severe loss of vision, hearing, or communicative abilities.

Randomization and Blinding

Cluster randomization was used to prevent contamination between participants going to the same community hospital, and assignment to either the multidomain intervention or usual care (i.e., control group) followed a 1:1 ratio. An independent researcher who was not involved in this study used computer-generated randomization procedure to conduct group allocation. Participants were blinded to the study design. Although at cluster level, allocation was not blinded to doctors and nurses at community hospitals, outcome assessments were administered by trained interviewers who were blinded to allocation and not involved in intervention activities.

Procedure

The intervention group received a multidomain training program consisting of mindfulness meditation, cognitive training, physical exercise, and nutrition counseling for 9 months (protocol is illustrated in Supplementary Fig. S1). The intervention was delivered with weekly group sessions at the community hospitals and self-monitoring homework that aimed to help participants practice what they learned on daily basis. Each group session usually took 1 hour, and homework was checked weekly by instructors.

Mindfulness meditation was delivered as one group session instructed by trained research assistants from the research team at the beginning of the intervention program, and then was practiced for 5 minutes repetitively at the beginning of each of the weekly group sessions. Participants were also required to practice it everyday as part of their homework. Cognitive training included 20 group sessions led by research assistants and weekly homework. The group sessions involved two sessions on educational information of age-related cognitive changes, 11 sessions on mnemonic strategies, four sessions on how to use smartphones, and three sessions on playing games involving the use of executive functioning, attention, and memory. Physical exercise training included two group sessions and daily homework. The group sessions were guided by licensed fitness instructors for doing aerobic exercise, strength, and balance. Nutrition counseling was conducted by physicians from the community hospitals, which involved one group session of educational lecture and two individual visits tailored for each participant, aiming to facilitate healthy dietary habits and risk management of cardiovascular diseases.

Due to the coronavirus disease 2019 (COVID-19) pandemic, the intervention was suspended for 15 weeks from January 2020 until May 2020, during which seven 10-minute review sessions were delivered through the Internet (WeChat application) or telephone to encourage participants to keep practicing. The last six group sessions (all about cognitive training) were transformed as an online format delivered through WeChat application or telephone using the same scripts. Also, participants were mailed with training materials and homework, and were contacted via WeChat or telephone by instructors weekly, so that they can keep up with the training schedule even during the pandemic.

Participants in the control group received usual care without any intervention components. All outcome assessments were administered at baseline, end of the intervention, and 1 year after completing the intervention.

Outcomes

A comprehensive battery was administered at the baseline, end of the intervention, and 1 year after completing the intervention (1-year follow-up). The primary outcome was change in cognitive performance measured by a composite cognitive Z score of seven cognitive tests, that is, MMSE, Montreal Cognitive Assessment (MoCA),[22] immediate, short-term and long-term delayed recall of Auditory Verbal Learning Test (AVLT),[23] recall of the easy and hard pairs of PALT, trail making test (shifting score B-A),[24] digit span backwards task from the Wechsler Adult Intelligence Scale,[25] and category fluency test.[26]

Secondary outcomes included domain cognitive Z scores for global cognition (MMSE & MoCA), episodic memory (AVLT & PALT), and executive functioning (trail making test, digit span backwards task, and category fluency test). Additional outcomes were subjective cognitive abilities, including cognitive complaints as measured by AD-8, everyday memory ability as measured by Prospective and Retrospective Memory Questionnaire,[27] and memory control beliefs as measured by Memory Controllability Inventory[28]; positive affective experiences as measured by a composite Z score of Satisfaction with Life Scale,[29] Index of Well-Being,[30] and Attitude toward Own Aging scale[31]; negative affective experiences as measured by a composite Z score of CES-D, Generalized Anxiety Disorder 7-Item Scale,[32] and UCLA Loneliness 8-Item Scale[33]; physical activity as measured by Physical Activity Scale for the Elderly[34]; dietary habits as measured by a healthy diet scale;[35] and social network size as measured by Lubben Social Network 6-Item Scale.[36]

Statistical Analysis

The sample size was estimated based on a power analysis for cluster trials using Power And Precision four to detect a difference in change of the overall cognition between the intervention and control group.[37] With an α of 0.05, a medium effect size of 0.4, and the

TABLE 1. Baseline Characteristics of Participants Included in the Modified Intention-to-Treat Analysis

Characteristics	Intervention (n = 86)	Control (n = 106)	$t/\chi 2$	p Value
Age	69.7 (6.0)	73.1 (5.7)	3.96	<0.001
Male, n (%)	22 (25.6)	36 (34.0)	1.92	0.209
Education (y)	8.0 (3.7)	9.0 (3.5)	1.58	0.056
APOE ε4 allele, n (%)	19 (22.1)	19 (17.9)	0.52	0.471
Cognition*	−0.016 (0.66)	0.055 (0.53)	0.83	0.408
Global cognition[a]	0.085 (0.81)	−0.020 (0.86)	0.87	0.388
Episodic memory[a]	−0.043 (0.83)	0.090 (0.65)	1.25	0.215
Executive function[a]	−0.042 (0.66)	0.034 (0.63)	0.81	0.420
Subjective cognitive complaints	3.73 (1.57)	3.45 (1.59)	1.22	0.223
Everyday memory	58.77 (9.95)	55.31 (10.80)	2.28	0.012
Memory control beliefs[a]	0.079 (0.56)	−0.044 (0.69)	1.33	0.174
Positive affect[a]	0.27 (0.55)	−0.25 (0.91)	4.90	<0.001
Negative affect[b]	−0.15 (0.74)	0.14 (0.70)	2.83	0.005
Physical activity	120.61 (60.01)	119.27 (59.90)	0.15	0.878
Dietary habits	21.55 (2.92)	20.87 (3.31)	1.49	0.138
Social network size	16.91 (6.44)	17.04 (6.04)	0.14	0.885

Note. n: sample size; Data are mean (standard deviation), unless otherwise specified. Means were compared with t tests ($df = 190$), and proportions were compared with $\chi 2$ test ($df = 1$, N=192).

[a] Scores are composite Z scores of the tests included in each outcome, with higher scores indicating better performance.

[b] Score is a composite Z score, with a higher value indicating a higher level of negative affective experiences.

consideration of intraclass correlation of 0.02, to achieve a power of 0.8, a minimum sample size of n = 90 per group (i.e., intervention & control) was required. For five communities per group, 18 participants per community were needed. Based on similar studies in local communities,[10,15] we assumed a dropout rate of about 15%, thus, a size of total 105 participants were needed for each group.

Analyses were conducted based on modified intention-to-treat (mITT) principle, such that participants who dropped out from the program were invited back at the end of the intervention and follow-up, and their data were included in analyses as long as they had at least one postbaseline assessment.[4,6] Natural log-transformation was performed on scores with skewed distributions in order to normalize the data. Z scores for tests at each time point were standardized to the baseline sample mean and standard deviation. Composite Z scores were obtained by averaging the individual component Z scores for corresponding outcomes or domains.

To examine the effects of the intervention on primary and secondary outcome measures, we used linear mixed-effects models with maximum likelihood estimation. To account for participant variability, random effects of intercepts and slopes for participant were assessed, and they were retained in the models if they were significant. Random effects for clusters (i.e., community hospitals) were also tested, however, they were never significant (Wald Z-test value < 1, p >0.1, intraclass correlation < 0.02) and ultimately dropped from all models. Time was treated as a categorical variable (baseline versus end of intervention versus follow-up). Models included fixed effects of group assignment, time, and the interaction of group and time. Sensitivity analyses were conducted with all cluster-randomized participants. Participants' baseline age and years of education, as well as variables that had group differences at baseline, were controlled as covariates in all analyses for examining the effects of the intervention (see details in Table 1).

Significant fixed effects were determined based on likelihood ratio tests (c^2), using a criterion of $p < 0.05$. Post-hoc tests were conducted to compare least squares means of interaction effects, and *p* values and confidence intervals (CIs) were presented with Tukey adjustment for multiple comparisons. Effect size was estimated using Hedges' *g* statistics. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc.).

RESULTS

Participant Flow and Adherence

As shown in Figure 1, between November 2018 and April 2019, 2,136 individuals were screened,

FIGURE 1. Flowchart of participants.

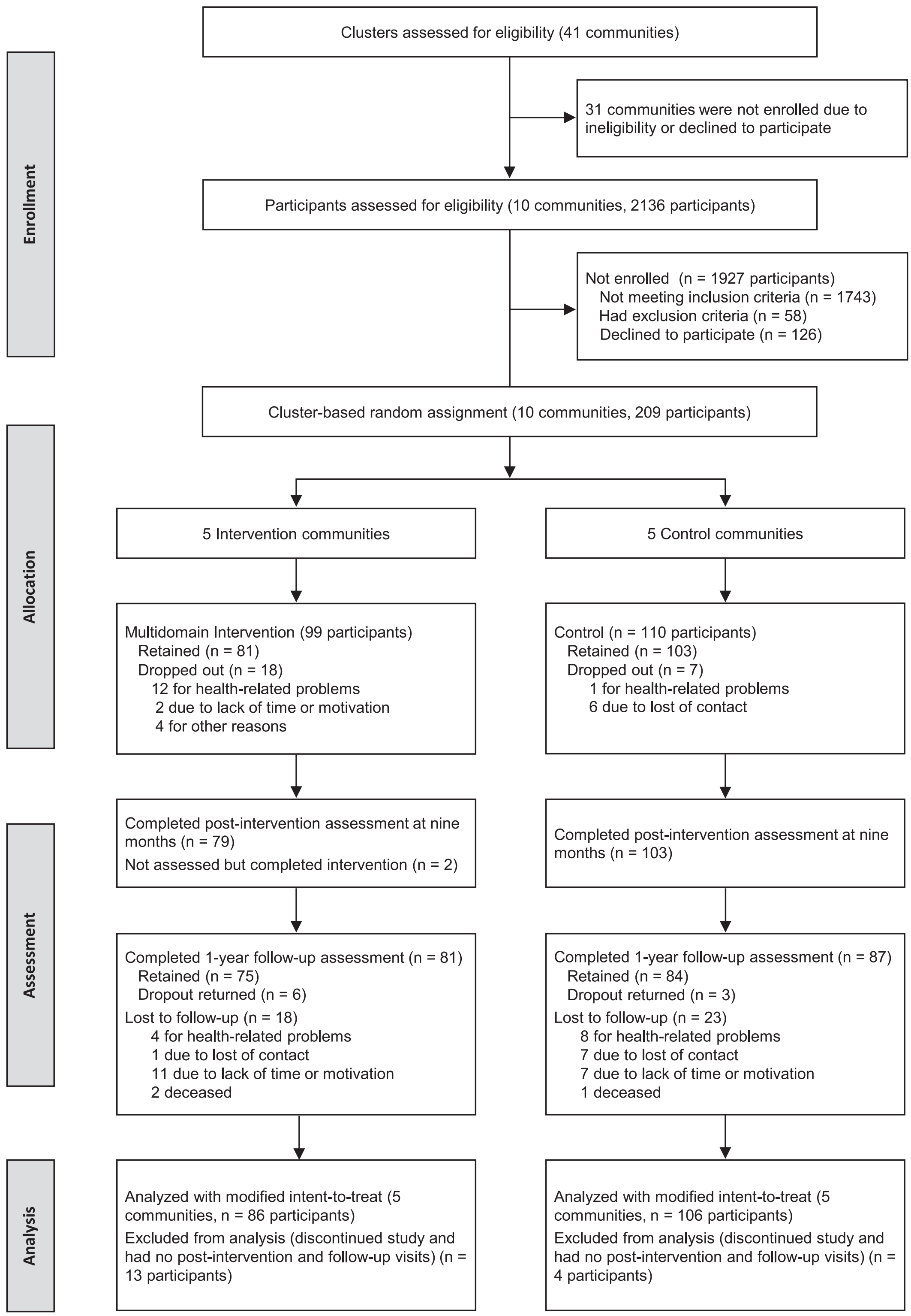
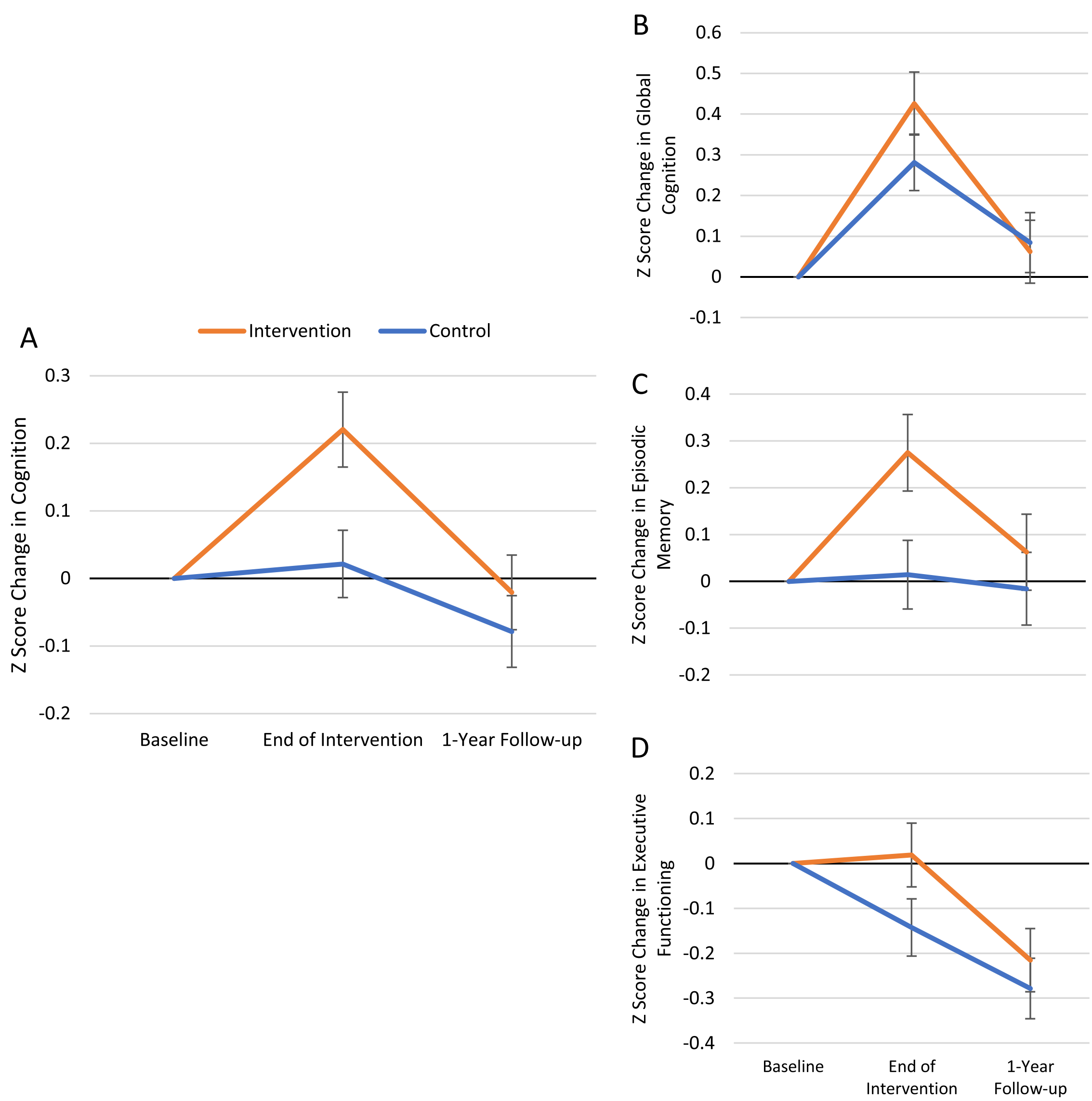


FIGURE 2. Estimated mean change of Z score in (A) cognition (primary outcome measured by seven cognitive tests), (B) global cognition, (C) episodic memory, and (D) executive functioning in the modified intent-to-treat sample, from baseline to end of intervention and 1-year follow-up (1 year after the completion of the intervention), for the intervention and control group. Error bars represent the standard errors of the mean change scores.



and the final sample consisted of 209 at-risk older adults from 10 community hospitals. The intervention started in September 2019 and was completed in June 2020, and the 1-year post-intervention follow-up was completed in August 2021. The mITT analysis included a total of 192 participants (91.9% of all enrolled participants) and excluded 17 participants.

The overall retention rate at the end of the intervention was 88.1%, with the intervention group having a relatively lower retention rate (81.8%) compared to the control group (93.6%), $\chi^2(1, N = 192) = 6.37$, $p = 0.01$. The overall rate for coming for the 1-year follow-up assessment was 80.4%, and there was no difference between the intervention (81.8%) and control group (79.1%). Of those who completed the

TABLE 2. Estimated Mean Change of Z Score From Baseline to the End of Intervention and From Baseline to 1-year Follow-Up (1 Year After the Completion of the Intervention) for the Intervention and Control Groups of the Modified Intention-to-Treat Sample

Outcome	End-of-Intervention Change From Baseline (Adjusted 95% CI)			1-Year Follow-Up Change From Baseline (Adjusted 95% CI)		
	Intervention	Control	Between Group Difference	Intervention	Control	Between Group Difference
Primary outcome						
Cognition	0.22 (0.061, 0.38)	0.021 (-0.12, 0.16)	**0.20 (0.053, 0.35)**	−0.021 (−0.18, 0.14)	-0.078 (-0.23, 0.073)	0.058 (-0.093, 0.21)
Secondary outcomes						
Global cognition	0.43 (0.20, 0.65)	0.28 (0.083, 0.48)	0.14 (−0.061, 0.35)	0.062 (−0.16, 0.28)	0.084 (−0.13, 0.30)	−0.022 (−0.23, 0.19)
Episodic memory	0.27 (0.040, 0.51)	0.014 (−0.17, 0.29)	**0.26 (0.045, 0.48)**	0.062 (−0.20, 0.22)	-0.016 (−0.24, 0.21)	0.077 (−0.14, 0.30)
Executive function	0.018 (−0.18, 0.22)	−0.14 (−0.33, 0.039)	0.16 (−0.026, 0.35)	−0.22 (−0.42, -0.014)	-0.28 (−0.47, −0.085)	0.062 (−0.13, 0.25)
Subjective cognitive complaints	−1.01 (−1.45, -0.57)	−0.32 (−0.71, 0.081)	**−0.70 (−1.10, -0.29)**	−0.92 (−1.36, -0.48)	-0.11 (−0.53, 0.31)	**−0.81 (−1.23, −0.39)**
Everyday memory	−0.15 (−0.45, 0.14)	0.10 (−0.16, 0.37)	−0.25 (−0.53, 0.015)	−0.092 (−0.39, 0.20)	0.11 (−0.17, 0.39)	−0.20 (−0.48, 0.079)
Memory control beliefs	0.14 (−0.079, 0.35)	0.078 (−0.11. 0.27)	0.058 (−0.14, 0.26)	0.21 (0.0019, 0.43)	0.0019 (−0.20, 0.21)	**0.21 (0.0074, 0.41)**
Positive affect	0.22 (0.00049, 0.43)	−0.062 (−0.26, 0.13)	**0.28 (0.079, 0.48)**	0.053 (−0.16, 0.27)	0.10 (−0.10, 0.31)	−0.051 (−0.26, 0.15)
Negative affect	−0.31 (−0.56, -0.049)	0.10 (−0.13, 0.33)	**−0.41 (−0.64, -0.17)**	−0.39 (−0.64, -0.13)	-0.35 (−0.59, −0.10)	−0.039 (−0.28, 0.20)
Physical activity	−0.086 (−0.41, 0.24)	−0.43 (−0.73, −0.14)	**0.35 (0.041, 0.65)**	−0.13 (−0.46, 0.20)	-0.49 (−0.80, -0.17)	**0.36 (0.046, 0.67)**
Dietary habits	0.27 (−0.036, 0.59)	0.0082 (−0.27, 0.29)	0.27 (−0.019, 0.55)	0.26 (−0.046, 0.57)	0.37 (0.083, 0.67)	−0.11 (−0.41, 0.18)
Social network size	0.032 (−0.27, 0.33)	-0.39 (−0.65, −0.12)	**0.42 (0.14, 0.69)**	0.18 (−0.11, 0.48)	-0.18 (−0.46, 0.10)	**0.36 (0.083, 0.64)**

Note. CI: confidence interval; Estimates were calculated from linear mixed-effects models with group, time, and group by time interaction as the fixed effects, and random intercepts for participant as random effects, while adjusting for age, years of education, baseline scores of everyday memory measure, and positive and negative affect measures. Estimated mean changes for between group differences in bold are significantly different from zero based on 95% confidence interval with Tukey adjustment for multiple comparisons.

intervention program, the attendance rate for group sessions was 71.4%; the homework completion rate for doing physical exercise, meditation, and cognitive training was 57.7%, 45.7%, and 49.6%, respectively. Participants were highly satisfied with the intervention, with scores of 2.94 and 2.91 out of three for in-person and online intervention delivery formats, respectively.

No study-related adverse events were reported from either the intervention or control group, and none of the participants was reported being infected with COVID-19 or quarantined during the pandemic.

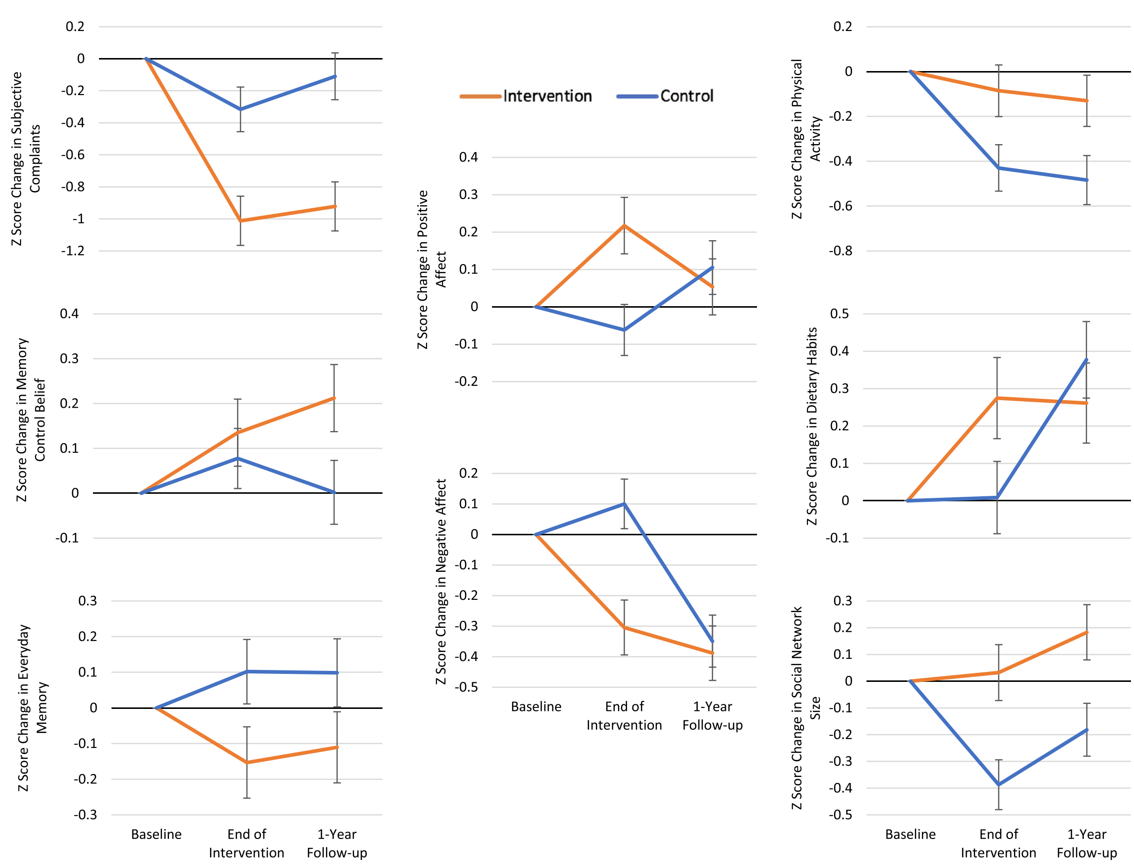
Baseline Characteristics

There were no significant differences between the participants who were included in and those were excluded from the mITT analysis in terms of age [t (207) = 1.08, p = 0.28], years of education [t (207) = 1.24, p = 0.22], gender composition [χ^2(1, N = 209) = 2.18, p = 0.14], *APOE* ε4 status [χ^2(1, N = 209) = 0.80, p = 0.78], level of cognitive ability [t (207)s < 1.23, p >0.22], and other measures [t(207)s < 1.75, p >0.08]. Table 1 presents the baseline characteristics of the mITT sample. Participants in the intervention group were younger but had a lower level of education attainment compared to those in the control group. The two groups did not differ significantly in the distribution of gender and *APOE* ε4 allele, and were similar in most of the outcome measures, except for everyday memory, and positive and negative affect.

Effects on Primary Outcome Measure

As illustrated in Figure 2A, there was a significant interaction of group and time on cognition, c^2(1, N = 192) = 4.94, p = 0.026. Table 2 shows that immediately after the 9-month intervention, the intervention group showed significant enhancement in cognitive performance from baseline, The between-group difference in the change of cognition was 0.20 (95% CI: 0.053, 0.35), with an effect size indicated by Hedges' g of 0.40 (95% CI: 0.29, 0.50), which can be considered clinically meaningful. However, this benefit did not persist at 1-year follow-up.

FIGURE 3. Estimated mean change of Z score in subjective cognitive abilities (left panel: subjective cognitive complaints, memory control beliefs, everyday memory), affective experiences (middle panel: positive affect, negative affect), and lifestyle factors (right panel: physical activity, dietary habits, social network), from baseline to end of intervention and 1-year follow-up (1 year after the completion of the intervention), for the intervention and control group. Error bars represent the standard errors of the mean change scores.



Effects on Secondary Outcome Measures

Figures 2B-D and 3 present the effects of intervention on secondary outcomes. Overall, there were several immediate benefits of the multidomain intervention, as indicated by significant group × time interactions found in episodic memory (c^2(1, N = 192) = 3.83, p = 0.05), subjective cognitive complaints (c^2(1, N = 192) = 9.98, p <0.001), positive affective experiences (c^2(1, N = 192) = 8.17, p = 0.004), negative affective experiences (c^2(1, N = 192) = 9.26, p = 0.002), level of physical activity (c^2(1, N = 192) = 4.49, p = 0.034), and social network size (c^2(1, N = 192) = 7.77, p = 0.005). Specifically, as indicated in Table 2, the intervention group showed improved episodic memory abilities, fewer subjective cognitive complaints, more positive affective experiences, fewer negative experiences, maintained levels of physical activity, and maintained social network size, relative to the control group. At the 1-year follow-up, some benefits of the intervention were retained for subjective cognitive complaints, memory beliefs, negative emotions, physical activity level, and social network. The benefits on other outcomes were no longer significant at the follow-up.

Sensitivity Analyses with All Cluster-Randomized Participants

Sensitivity analyses were conducted with all cluster-randomized participants, with missing values imputed using the Markov chain Monte Carlo method with five imputations. The baseline participants characteristics are presented in Supplementary Table S1. As indicated in Supplementary Table S2, results from linear mixed-effects models investigating the effects of intervention on primary and secondary outcomes showed the same pattern with those from the mITT approach.

CONCLUSIONS

The COMBAT study was the first clinical trial of a multidomain intervention conducted in metropolitan communities in China, aiming to improve cognitive abilities for at-risk older adults. Findings showed that this community-based intervention had immediate efficacy in improving overall cognitive performance, episodic memory, subjective cognitive abilities, affective experiences, and lifestyle factors. These supported the view that interventions targeting multiple factors could benefit cognitive function among community-dwelling older adults at risk of cognitive decline, which was consistent with the WHO guidelines.[38] Even though the current study targeted at-risk individuals in the communities rather than patients in clinical settings, the intervention effect (between-group difference of Z score of 0.20, Hedges' *g* of 0.40) was clinically meaningful. As pointed out in the literature, an effect size of 0.20 in nonpharmacological cognition-focused intervention is comparable with those of clinical trials with pharmacological treatments for cognitive impairment.[39]

It is important to highlight that the immediate effects on improving cognition were largely attenuated at the 1-year follow-up, suggesting the long-term effects could be hard to achieve without continuous training. This issue is critical to intervention studies, and future research should pay more attention to evaluating the long-term effects and considering approaches to maintain the training effect. In the current study, the lack of benefits at follow-up might be due to the relatively low intensity and short duration of current study, compared to other multidomain intervention trials.[3–7] As there is no consensus on the optimal dosage of multidomain intervention, this speculation deserves further careful investigation. Alternatively, booster training sessions can be provided, so that the intervention effect can be maintained with relatively low training intensity. However, we noted that the effects on subjective cognitive abilities were maintained. These could still imply that this trial had some lasting effects, since subjective cognitive abilities are usually associated with objective cognitive abilities,[40] and the complaints serve as an early indicator of cognitive impairment.[41] In addition, relative to the control group, the intervention group had less significant decline in some lifestyle factors (i.e., physical activity and social network) at the follow-up. Although we were not able to draw a firm conclusion on the long-term effects, possibly the benefits of multidomain intervention could persist to some extent.

The target of this study was at-risk individuals, who were identified with the use of several risk factors from various aspects, such as demographic information, lifestyle, neuropsychological test scores, and *APOE* ε4 genotypes. However, it should be noted that we did not give clinical diagnoses during screening but used MMSE and PALT scores, so it is possible that some participants might already had early signs and pathological brain changes. This could be improved in future studies with more sophisticated screening criteria.

One of the strengths of this intervention was the incorporation of mindfulness meditation. Though the underlying mechanisms are not fully understood, the involvement of meditation training might help older adults reduce negative affect, which would lead to positive changes in physiological systems (e.g., hypothalamic pituitary adrenal axis) and brain regions,[42] and could ultimately benefit cognitive function. Thus, future studies of multidomain lifestyle interventions would consider having emotion management training component, such as meditation, stress management, or emotion-based therapies, and further investigate its contribution to cognition improvement.

Another strength was the combined delivery method (group training & self-monitoring homework). Although it was a relatively novel approach for conducting intervention trials, it has demonstrated a good potential to be adopted for future studies. This combined method might be more suitable when intense in-person training is hard to achieve, for instance, during the pandemic. Even with the occurrence of an unexpected catastrophe (i.e., COVID-19) that threatened study implementation,[43] the adherence was good as more than 80% of participants completed the intervention and returned for post-tests, and participants were highly satisfied with both in-person and online format of training.

The potential limitations of our study deserve discussion. First, the number of clusters was limited, which could lead to the different baseline characteristics for the intervention and control group. Second, a usual care group was used as the control, but the more ideal design would be to use an active control for a better comparison to examine the cognitive benefits of the intervention group. Third, there was a differential retention rate for the intervention and control group, which would need further examination. Furthermore, the lack of maintenance of training effects on cognitive performance by the 1-year follow-up suggested that it may be necessary to extend the intervention duration and include booster sessions. The intervention curriculum, especially on cognitive training, may be further modified for training cognitive skills that can be applied in daily activities, and assessment should include more measures for cognitive performance in real-life scenarios. Lastly, more investigations are needed to explore the individual differences in response to the intervention. One approach would be to examine how training gains can be moderated by participant characteristics, such as demographic profiles, adherence to training, and baseline performance. Another approach would be to design "precision intervention," that is to develop personalized training programs that are tailored to each person's needs.

In summary, this intervention study demonstrated the short-term efficacy of community-based multidomain intervention to improve cognition among Chinese older adults who were at risk of cognitive decline. The long-term effects of multidomain interventions on cognitive function and cognitive impairment risk warrant further investigation.

AUTHOR CONTRIBUTIONS

Study conception and design: Z. Ma, X. Zhu, Z. Zheng, Z. Wang, Z. Yin, C. Qiu, and Juan Li. Acquisition of data: Z. Ma, Jing Li, J. Fu, Q. Shao, X. Han, and X. Wang. Analysis and interpretation of the results: X. Liu, Z. Ma, X. Zhu, and Juan Li. Preparation of the manuscript: all authors prepared the manuscript (X. Liu wrote the original draft, and all authors reviewed the final manuscript). Study supervision: Juan Li.

DATA STATEMENT

The data has not been previously presented orally or by poster at any scientific meetings.

DISCLOSURES

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The authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2022.10.006.

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