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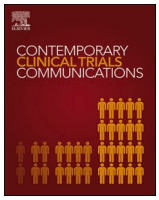

Efficacy of a non-pharmaceutical multimodal intervention program in a group setting for patients with mild cognitive impairment: A single-arm interventional study with pre-post and external control analyses

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ABSTRACT

Aim: This study aimed to evaluate the efficacy of a non-pharmaceutical multimodal intervention program consisting of physical exercise, cognitive stimulation, and health education in a group setting to slow the progression of mild cognitive impairment (MCI).

Methods: A single-arm interventional study was conducted on 27 patients with MCI. To evaluate the efficacy of the intervention program, a pre-post analysis was performed using EuroQol-5 Dimension (EQ-5D), Mini-Mental State Examination (MMSE), Cognitive Function Instrument (CFI), 5 Cog test, depression, and physical performance before and after the 8-month intervention. Additionally, propensity score and the semi-Bayes analyses were performed to compare the intervention program with standard medical care, using the external control patients' data for MMSE scores.

Results: Twenty-four patients completed the intervention program. During the study period, although EQ-5D and MMSE scores remained unchanged (mean change 0.02 [95 % confidence interval (CI): −0.004, 0.04], 0.5 [-0.2, 1.3]), CFI and the subcategories of 5Cog (attention and reasoning) improved (mean change −1.23 [-2.24, −0.21], 4.3 [0.9, 7.7], 3.0 [0.4, 5.6]). In the additional analysis comparing changes in MMSE scores, patients who underwent the intervention program had less decline than the external control patients (mean change −1.7 [-2.1, −1.3]) with an observed mean difference of 2.25 [1.46, 3.03], and propensity score-adjusted difference of 2.26 [1.46, 3.05]. The semi-Bayesian approach also suggested that the intervention slowed the progression of MCI.

Conclusion: A non-pharmaceutical multimodal intervention program could contribute to slowing cognitive decline in patients with MCI.

1. Introduction

Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive function and dementia, the concept of which was proposed by Petersen [1]. The prevalence of MCI increases with age and is reported to be 15–25 % in people aged ≥65 years [2,3]. With an unprecedented increase in elderly population, social burdens associated with MCI and dementia have become a pressing challenge in many countries, including Japan [4].

Currently, non-pharmaceutical therapeutic strategies, including physical exercise, cognitive stimulation, and combination programs, are being vigorously investigated to prevent the progression of MCI [5–7]. For instance, Barnes et al. reported improvement of global cognitive function in inactive older adults after a 12-week physical and mental

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activity intervention [6]. Further, Kajita et al. reported that a multimodal intervention program consisting of physical exercise, cognitive training, dual-task training, and nutritional education was beneficial for improving or maintaining the cognitive and physical function of community-dwelling elderly individuals at high risk for MCI/dementia [7]. Furthermore, several systematic reviews and meta-analyses have shown that combined cognitive and physical exercise programs may be more effective than cognitive or physical exercise alone, since they could affect a variety of underlying conditions related to dementia [8,9].

However, the simultaneous implementation of non-pharmaceutical therapies, such as exercise and cognitive training, could be difficult for a large number of patients compared to pharmacologic therapies, in part due to the high burden on training providers. Indeed, whether non-pharmaceutical therapy programs are acceptable in practice is crucial, and the community-based intervention programs in a group setting could serve as a solution, because they can be simultaneously provided to more patients with less labor, reducing the burden on the program provider. However, there is insufficient evidence regarding the methodologies and efficacy of non-pharmaceutical interventions in group settings, for the maintenance of cognitive function.

In this study, we explored the efficacy of a multimodal intervention program in the form of group activities comprising physical exercise, cognitive stimulation, and health education lectures, to slow the progression of MCI.

2. Materials and methods

2.1. Study design

This single-arm, prospective study of a non-pharmaceutical intervention program to prevent cognitive function decline, was performed by enrolling patients diagnosed with MCI at the Center for Memory and Behavioral Disorders, Kobe University Hospital, between November 2017 and September 2018. The diagnosis of MCI was based on the National Institute on Aging and Alzheimer's Association "Guidelines for Diagnosis of MCI" [10], and was performed by neurologists specialized in the neuropsychological assessment of dementia/MCI.

The inclusion criteria were as follows: 1) aged 50–85 years, 2) spending at least 10 h a week with a partner, 3) consent to visit the outpatient clinic regularly and undergo cognitive function and other questionnaire-style tests, and 4) no complications or paralysis requiring restrictions on exercising.

The study protocol (UMIN000044224) was approved by the ethics committee of the Kobe University Graduate School of Health Sciences (approval number 595). The study conforms to the provisions of the Declaration of Helsinki and was conducted in accordance with Japan's "Ethical Guidelines for Medical and Health Research Involving Human Subjects." Written informed consent was obtained from all the patients.

Additionally, this study was conducted in association with the "Kobe Project for the Exploration of Newer Strategies to Reduce the Social Burden of Dementia" [11], which was a collaborative research project between Kobe University and the World Health Organization.

2.2. Intervention

The participants underwent a series of intervention programs (three times/month) lasting for 8 months (Supplement 1).

The intervention program was conducted in a group setting. One class consisted of 30 min of physical exercise, 20 min of lecture, and 40 min of group work, the detail of which is described in Fig. 1. For physical exercise, the participants underwent aerobic exercise and muscle training while their pulse rate was measured to control the exercise intensity to suit each individual under the supervision of a research assistant. During the lectures, participants were educated by a research assistant on lifestyle factors thought to mitigate MCI progression, including exercise, diet, nutrition, sleep, intellectual activity, and oral healthcare (Supplement 2). Group work was conducted at the end of each class under the supervision of the research assistant, wherein the participants reviewed and discussed the lecture of the day and their daily lives to increase their understanding of their disease and therapies.

2.3. Evaluation measures

Health-related quality of life (HR-QoL), cognitive performance, depression, and physical performance were evaluated in all patients before and after the 8-month intervention.

In this exploratory study, the primary outcome was set to be HR-QoL as assessed by the EQ-5D-5L, to comprehensively evaluate the efficacy of the multimodal intervention in patients with MCI. The EQ-5D-5L is one of the most frequently used non-disease-specific instruments for evaluating HR-QoL [12], and several reports have shown that EQ-5D scores are lower in patients with dementia and MCI than in healthy controls [13,14].

As other outcomes, cognitive performance was assessed using three measures; Mini-Mental State Examination (MMSE) [15], Cognitive Function Instrument (CFI) [16], and the 5-Cog Battery for Detecting Cognitive Impairment and Dementia [17]. The MMSE is a standard measure of cognitive function, widely used across the world. The CFI is a questionnaire developed as a screening test for detecting earlier impairment of activities of daily living (ADL) due to cognitive decline; it is a simple tool for assessing functional abilities in earlier stages of cognitive decline [18,19]. The 5Cog is a tool for simple screening of cognitive functions in the Japanese population and correlates well with other established tests, such as A Quick Test of Cognitive Speed, Trail Making Test, Wechsler Adult Intelligence Scale (3rd edition), and Wechsler Memory Scale [17]. Additionally, the state of depression was

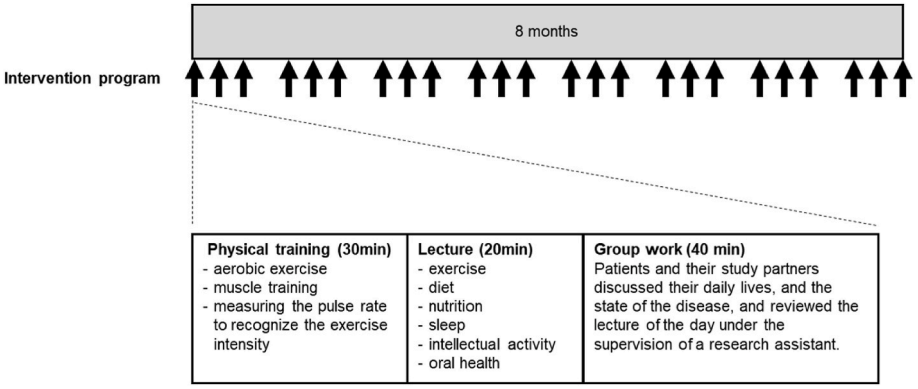

Fig. 1. Timetable of the therapeutic program. The participants attended 24 classes that lasted 90 min/day, 3 days/month, for 8 months. One class consisted of 30 min of physical exercise, 20 min of lecture, and 40 min of group work.

evaluated using the Geriatric Depression Scale (GDS) [20]. Also, physical performance was evaluated with grip strength and the timed up and go test (TUG) [21].

2.4. External control data

To further investigate the efficacy of the intervention program on cognitive performance, MMSE, age, and sex data were collected from patients with MCI who were diagnosed at the Kobe University Hospital between 2016 and 2018 and who received standard medical care, to be used as the external control. Data from all patients who underwent MMSE evaluations twice, at diagnosis and after 6–8 months, were analyzed. The use of such external control data was approved by the ethics committee of Kobe University Hospital (approval number 180334-15) and opt-out consent approach was adopted according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects of Japan.

2.5. Statistical analyses

The number of subjects was planned to be 50 based on feasibility. Because this was a highly exploratory study, with no available prior information regarding the effect size of intervention in EQ-5D-5L, no statistical power analysis was conducted.

Baseline characteristics of subjects are shown as mean (standard deviation [SD]) and median (min, max) for continuous data, and frequency and proportion for categorical data.

The main analyses of changes from baseline were performed for subjects who received the intervention. For primary and secondary outcomes, the mean changes in variables between before and after the intervention, and their 95 % confidence intervals (CI) were estimated. One-sample paired t-tests were performed with a two-tailed significance level of 5 %.

As an additional post hoc analysis, we attempted to compare the change in MMSE scores in patients who received the intervention with those in the external control group. The adjusted mean difference of this change was estimated using a linear regression model. The change in the MMSE score was the response variable (Y), and the group variable ($x = 1$ for the current study patients or $x = 0$ for external control patients) and propensity score (PS) consisting of two measured baseline variables – sex (z_1) and age (z_2) – as explanatory variables were included in this model:

$$Y_i = \alpha + \beta x + \gamma \widehat{e}_i + \varepsilon_i,$$

where α, β, and γ were parameters, $\widehat{e}_i$ was the estimated PS with parameters α^*, γ_1^*, and γ_2^*, $\widehat{e}_i = \frac{exp\left(\widehat{\alpha^*} + \widehat{\gamma_1} z_{1i} + \widehat{\gamma_2} z_{2i}\right)}{1 + exp\left(\widehat{\alpha^*} + \widehat{\gamma_1} z_{1i} + \widehat{\gamma_2} z_{2i}\right)}$, and ε_i was the error following $N\left(\mu_i, \sigma^2\right)$. Since the adjustment for age and sex alone could be insufficient in a comparison with the external control group, an additional analysis was conducted using the semi-Bayes method based on the data augmentation prior (DAP) to obtain conservative estimated values. A DAP enables approximate Bayesian analyses using the usual frequentist statistical software. When a DAP is applied to a mixed-effects model, a partial Bayesian regression called a semi-Bayes analysis can be performed. For the semi-Bayes analysis of β, we assumed the prior distribution of $N\left(\beta_0,\ \sigma_\beta^2\right)$. To lead the posterior distribution of β, we needed to calculate the following:

$$p(\beta|y) \propto exp\left(- \frac{\sum_i (y_i - \mu_i)^2}{2\sigma^2} \right) exp\left(- \frac{(\beta - \beta_0)^2}{2\,\sigma_\beta^2} \right)$$

$$= exp\left(- \frac{\sum_i (y_i - \mu_i)^2 + w(\beta_0 - \beta)^2}{2\sigma^2} \right),$$

where $w = \sigma^2 / \sigma_\beta^2$. To obtain the posterior mode of this distribution of β, we had to obtain β to maximize the above probability $p(\beta|y)$; to accomplish this, we used the weighted least square method that is implemented by statistical software to conduct linear regression analyses. This semi-Bayes method, based on the DAP, can be applied by adding a single row of data to a dataset with weights for a weighted regression analysis. This additional row consists of the value of β_0 as the response variable, one as the group variable, zero for the intercept term and other variables as the explanatory variables, and a weight value as the size of the prior information. For this DAP analysis, the value of β_0 and the weight, w, required specification. The value β_0 was set at 0 because we needed to estimate the shrinkage mean differences of the change in MMSE score toward no effect to obtain the adjusted mean differences as a conservative estimate. Weight w is equal to the effective sample size of the prior information. If w is set to 0, the prior information is not used; if the w value is large, the estimate of β is changed to β_0. The influence of the strength of the prior information could be estimated using this method, as different weight values lead to different estimated values of β. As described above, the w value was related to σ_β, which is referred to here as the SD of the prior distribution of the adjusted difference. To estimate σ_β, we first obtained $\widehat{\sigma}$ by fitting the above regression model to the dataset before inserting the additional row and then calculated $\sqrt{\widehat{\sigma}^2 / w}$. The details of the semi-Bayes method are described in section 14.8 of Gelman et al. [22]. This method may be applicable to various situations where the setting of a parallel control group is difficult owing to ethical issues and the rarity of the patients.

All statistical analyses were performed using R software version 4.1.2.

3. Results

3.1. Patient characteristics

Twenty-seven patients were enrolled in the intervention group (Fig. 2). Because one patient withdrew consent and two patients did not complete the 8-month intervention, the remaining 24 patients (age: 74.5 ± 6.0 years, male: 50 %) were included in the analyses. The mean (SD) of MMSE and CFI at the baseline were 23.9 (3.3) and 4.44 (3.36), respectively (Table 1). As a reference, external control data were obtained from 44 patients (age: 75.9 ± 6.0 years, male: 43.2 %).

3.2. Primary and secondary outcomes

The EQ-5D score did not change after the intervention compared to that before the intervention (mean change 0.02 [95 % CI: −0.004, 0.04], n = 22), while the CFI score improved (mean change −1.23 [95 % CI: −2.24, −0.21], n = 22). As the standard measure of cognitive function, MMSE did not noticeably decrease (mean change 0.5 [95 % CI: −0.2, 1.3], n = 24) (Table 2). Moreover, among the subcategories of the 5Cog

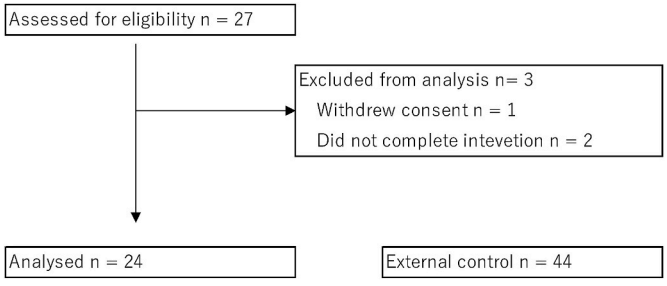

Fig. 2. Twenty-seven patients were initially enrolled in this study. Because 1 patient withdrew consent and 2 patients did not complete the 8-month intervention, the remaining 24 patients (age: 74.5 ± 6.0 years old, male 50 %) were included in the analyses.

Table 1
Subject characteristics.

		Intervention	External control
		(n = 24)	(n = 44)
Age (years)[a]	mean (SD) median (min, max)	74.5 (6.0) 73.5 (61.0, 87.0)	75.9 (6.0) 76.0 (53.0, 84.0)
Sex (Male(%))		12 (50.0 %)	19 (43.2 %)
EQ-5D[a]	mean (SD) median (min, max)	0.92 (0.10) 1.00 (0.75, 1.00)	– –
MMSE[a]	mean (SD) median (min, max)	23.9 (3.3) 24.0 (16.0, 29.0)	25.7 (2.1) 26.0 (21.0, 29.0)
CFI[a]	mean (SD) median (min, max)	4.44 (3.36) 4.75 (0.00, 12.50)	– –
5Cog[a]			–
Attention	mean (SD) median (min, max)	41.3 (10.0) 40.0 (17.0, 58.0)	– –
Memory	mean (SD) median (min, max)	31.0 (8.1) 29.5 (20.0, 55.0)	– –
Visuospatial function	mean (SD)	53.0 (5.5)	–
	median (min, max)	54.0 (35.0, 62.0)	–
Language	mean (SD) median (min, max)	37.8 (9.6) 37.0 (19.0, 58.0)	– –
Reasoning	mean (SD) median (min, max)	42.8 (8.7) 41.0 (32.0, 64.0)	– –
GDS[a]	mean (SD) median (min, max)	3.8 (3.2) 3.0 (0.0, 10.0)	– –
Grip strength (kg)[a]	mean (SD) median (min, max)	26.10 (9.29) 23.65 (13.25, 43.75)	– –
Timed up & go (second)[a]	mean (SD)	6.85 (2.37)	–
	median (min, max)	6.14 (4.38, 12.56)	–

Values in parentheses are percentages unless indicated otherwise.
SD: standard deviation, EQ-5D: EuroQol-5 Dimension, MMSE: Mini-Mental State Examination: CFI: Cognitive Function Instrument, GDS: Geriatric Depression Scale.
[a] values are mean (SD).

test, the attention score and the reasoning score tended to improve after intervention (mean change 4.3 [95 % CI: 0.9, 7.7] and 3.0 [95 % CI: 0.4, 5.6], respectively; n = 22). Additionally, as measures of depression and physical performance, GDS, grip strength, and TUG were similar before and after the intervention.

3.3. Additional analyses

Among the external control patients who received standard care, the mean (SD) MMSE score was 25.7 (2.1) initially and 24.0 (2.3) after 6–8 months, with a mean decline of −1.7 [95 % CI: −2.1, −1.3, n = 44]. When the decline of MMSE score was compared between patients who received the intervention and external control patients without intervention, patients with intervention had a smaller decline in score than that of the external controls (observed mean difference 2.25 [95 % CI: 1.46, 3.03]), and the difference persisted after adjusting for age and sex (propensity score-adjusted mean difference 2.26 [95 % CI: 1.46, 3.05]).

Fig. 3 shows the adjusted mean difference of the change in MMSE score for the prior belief of no effect using the semi-Bayes method, in which $\widehat{\sigma} = 1.58$. As observed in Fig. 3, the adjusted mean difference of change in MMSE [95 % Bayesian confidence interval (credible interval)] was 2.12 [1.33, 2.91] when the weight was 1, and the smaller the weight, the closer the mean difference was to 2.26, which was the propensity score-adjusted mean difference. The shrinkage mean differences with several prior SDs showed positive values of the estimated effect for most, even in a conservative condition; 0.13 [95 % credible interval: −0.10, 0.36] at 0.1 of the SD of the prior distribution.

4. Discussion

The major findings of the current study are as follows: 1) a non-pharmaceutical multimodal intervention program consisting of physical exercise, cognitive stimulation, and health education lectures can have a favorable effect on the maintenance of cognitive function in patients with MCI; 2) based on the changes in MMSE scores observed in this study, the intervention program could slow the progression of MCI compared to external control with standard care, as evidenced by propensity score analysis and semi-Bayes method analysis.

4.1. Characteristics of subjects

In this study, the baseline characteristics of our study patients were similar to those of general patients with MCI in Japan [23,24], and to those of external control patients who received standard care outside of this study. These findings would allow for the extrapolation of our findings to the general patients with MCI in our country.

Based on feasibility, the number of subjects was initially set as 50. However, we could only recruit approximately half the number of patients, predominantly due to the greater than expected difficulty, in finding eligible patients who could spend at least 10 h/week with the study partner, which reduced the robustness of our findings.

4.2. Adherence to the intervention

Because compliance and adherence to the intervention are essential to achieve meaningful improvements, various types of support strategies were previously examined; group-based intervention is thought to be a useful strategy for dementia and MCI [25,26]. In the current study, 24 (88 %) of the 27 patients who enrolled, completed the 8-month intervention. This percentage appears to be higher compared to that in similar studies assessing non-pharmaceutical interventions for MCI [25]. In our intervention program, the intensity of the exercise was personalized according to patient characteristics to achieve better compliance, and active incorporation of group work was adopted for adherence. This approach may have contributed to the relatively high completion rate observed in this study.

4.3. Efficacy on cognitive decline

In this study, the MMSE score remained unchanged over the 8-month intervention. In addition, a tendency toward improvement was observed for CFI as well as for attention and reasoning in the 5Cog test (Table 2). It is generally known that cognitive function progressively declines in patients with MCI. For instance, in Japan-Alzheimer's Disease Neuroimaging Initiative (ADNI) [23], a multicenter longitudinal observational study on Alzheimer's disease, the MMSE score declined by 1.52 points/year over 3 years in patients with late amnestic MCI, with a greater change in the first 6 months. In light of this observation, the current intervention program could have contributed to the maintenance of cognitive performance in patients with MCI, although we could not directly compare it with concurrent controls.

Table 2
Mean change of outcomes.

	Pre		Post		Change		t-value	p-value
	n	mean (SD)	n	mean (SD)	n	Mean Change [95 % confidence interval]		
EQ-5D	24	0.92 (0.10)	22	0.93 (0.10)	22	0.02 [-0.004 to 0.04]	1.72	0.100
MMSE	24	23.9 (3.3)	24	24.4 (3.8)	24	0.5 [-0.2 to 1.3]	1.50	0.147
CFI	24	4.44 (3.36)	22	3.11 (3.09)	22	−1.23 [-2.24 to −0.21]	−2.51	0.020
5Cog								
Attention	24	41.3 (10.0)	22	46.1 (10.1)	22	4.3 [0.9 to 7.7]	2.62	0.016
Memory	24	31.0 (8.1)	22	32.2 (9.3)	22	1.4 [-0.4 to 3.1]	1.64	0.117
Visuospatial function	24	53.0 (5.5)	22	51.2 (9.3)	22	−1.6 [-6.5 to 3.3]	−0.67	0.509
Language	24	37.8 (9.6)	22	39.4 (9.7)	22	2.0 [-1.5 to 5.6]	1.20	0.245
Reasoning	24	42.8 (8.7)	22	45.8 (8.3)	22	3.0 [0.4 to 5.6]	2.44	0.024
GDS	24	3.8 (3.2)	22	3.6 (3.0)	22	−0.4 [-1.1 to 0.4]	−1.00	0.329
Grip strength (kg)	24	26.10 (9.29)	24	25.67 (9.23)	24	−0.43 [-1.47 to 0.62]	−0.85	0.407
Timed up & go (second)	24	6.85 (2.37)	24	7.09 (2.42)	24	0.23 [-0.03 to 0.50]	1.81	0.084

*Values are mean (SD).
SD: standard deviation, EQ-5D: EuroQol-5 Dimension, MMSE: Mini-Mental State Examination: CFI: Cognitive Function Instrument, GDS: Geriatric Depression Scale.

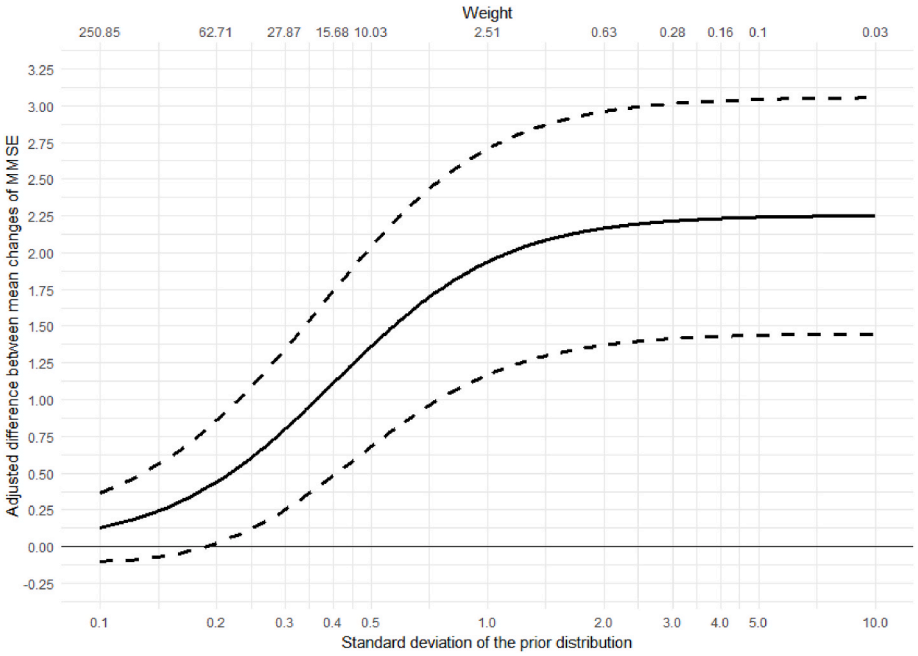

Fig. 3. The vertical axis is the adjusted mean difference of MMSE (solid line) and the upper and under limits of the 95 % credible interval (dashed lines); the horizontal axis is the standard deviation (SD) of the prior distribution of the adjusted difference, and the weight which is the inverse of the squared of the SD of the prior distribution. The mean of the prior distribution of the adjusted is zero in this semi-Bayes analysis because it is considered that the mean difference of changes in MMSE scores between the intervention and the external control affects the unmeasured confounders and the estimated adjusted mean difference in suspected bias by systematic error. As we cannot know the size and direction of the bias, we set the mean of the prior distribution to zero, that is, no effect. The smaller the value of the SD of the prior distribution, the stronger belief of the no difference between the two means. The weight is calculated using SD of prior distribution, which indicates the number of additional subjects for the prior belief of no effect in this analysis. When the weight was 1, the adjusted mean difference of changes in MMSE score was 2.12 [95 % credible interval: 1.33 to 2.91], and the smaller the weight was <1, the closer the mean difference was to 2.26, which is the propensity score-adjusted mean difference. At 0.1 of the SD of the prior distribution, i.e., 251 of the weight, the adjusted mean difference of change in MMSE score was 0.13 [95 % credible interval: −0.10 to 0.36]: At 0.5 of the SD, i.e., 10 of the weight, the adjusted mean difference was 1.36 [95 % credible interval: 0.68 to 2.04].

Additionally, some studies have reported that HR-QoL, depression, and physical performance are associated with cognitive decline. However, in this study, EQ-5D scores did not change after the intervention (Table 2). Because EQ-5D is a comprehensive measure based on subjectivity, more disease-specific measures might have been appropriate for assessing HR-QoL in patients with MCI, particularly for detecting slight changes in HR-QoL in patients with early MCI. In addition, no changes in depression and physical performance were detected before or after the intervention (Table 2). However, the sample size of this study was inadequate, limiting the implications of these findings.

4.4. Comparison to external control data

To further address to the effects of our intervention program on cognitive function, an additional post hoc analysis was performed using external control data. We found that patients who received the intervention had less decline in MMSE than those who did not, and the difference persisted after adjusting for age and sex using propensity score analysis. These findings support the beneficial effects of our intervention program on the maintenance of cognitive function in patients with MCI. To reinforce this finding, the mean shrinkage difference in the change in MMSE score toward zero was estimated using the semi-Bayes method (Fig. 3). Since the value of the prior SD was unknown, it was

hypothesized as 0.36, which was the standard error of change in MMSE score in the intervention patients, resulting in the adjusted difference of 1.00 [95 % credible interval: 0.39, 1.59] (Fig. 3). Even when half the standard error value was used, the positive adjusted difference persisted. Taken together, these findings suggest that our intervention program could aid in slowing the progression of MCI, which is in line with previous studies on non-pharmaceutical multimodal interventions for patients with MCI [8,9].

4.5. Limitations

This study has some limitations. First, the effects of the intervention could not be accurately estimated because there was no concurrent comparison group. Under such conditions, we conducted propensity score and semi-Bayes method analyses using external control data. Although these were not preplanned analyses, the derived results may reinforce the authenticity of our findings. Notably, such an approach can be applicable to single-arm studies of different environments or other disease areas, when the setting of concurrent control is difficult due to various reasons, extending the potential utility of our analyses. Second, because of the difficulty in finding study partners who could attend every class, as required by the eligibility criteria, the sample size was smaller than initially expected; therefore, studies with larger sample sizes are required to increase the reliability of our findings. Third, although our intervention program appeared to have some efficacy for a certain group of patients with MCI, it may not be optimized to exert maximum effects. Even under such conditions, the intervention program conducted in this study may be feasible in a community setting and is likely to have a certain effect to slow the progression of cognitive decline; it should therefore be tested in larger studies with confirmatory designs.

5. Conclusions

The 8-month non-pharmaceutical multimodal group-based intervention program consisting of physical exercise, cognitive stimulation, and health education lectures could contribute to slowing cognitive decline, which may have potential utility for maintaining cognitive performance in patients with MCI. Further studies with concurrent controls are required to clarify the effects of the intervention programs.

Role of the funding source

The multimodal intervention program conducted in this study was provided by the NPO Dementia Prevention Net Kobe, the conduction of which was financially supported by the "Kobe Project for the Exploration of Newer Strategies to Reduce the Social Burden of Dementia", a collaborative research project between Kobe University and the World Health Organization, Switzerland. This study utilized the data accumulated through the activity of the NPO, and did not receive monetary support from any organizations.

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CRediT authorship contribution statement

Satoshi Nakagawa: Writing – original draft, Data curation, Conceptualization. **Hisatomo Kowa:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Yumi Takagi:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Data curation. **Yasumasa Kakei:** Writing – review & editing, Supervision, Conceptualization. **Tatsuo Kagimura:** Writing – review & editing, Supervision. **Shoji Sanada:** Writing – review & editing, Supervision. **Yoji Nagai:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2024.101326.

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