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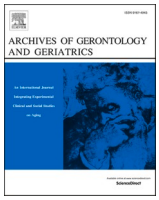

The Japan-Multimodal Intervention Trial for Prevention of Dementia PRIME Tamba (J-MINT PRIME Tamba): Study protocol of a randomised controlled multi-domain intervention trial

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ABSTRACT

The Japan-Multimodal Intervention Trial for Prevention of Dementia PRIME Tamba (J-MINT PRIME Tamba) is a randomised controlled trial to prevent cognitive decline in community-dwelling cognitively ordinary older people at risk of dementia. Participants are aged 65–85 years living in a rural area in Japan, aware of very mild decline in cognitive function or abilities of activities of daily living, have at least one vascular risk (e.g. hypertension or diabetes), and have a Mini-Mental State Examination score of 24 or higher. Approximately 200 participants are randomly divided into two groups, with the intervention group receiving a multi-modal intervention, including lifestyle-related disease management, physical exercise, cognitive training, and nutritional counselling, over 18 months. The primary outcome is change in the composite score of seven neuropsychological tests, including the Free and Cued Selective Reminding Test, Logical Memory I and II subsets of the Wechsler Memory Scale-Revised, and Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale. In addition, changes in a wide range of other parameters such as physical function, blood test results, sleep, and frailty are also analysed as secondary outcomes. We believe that this study's results will contribute significantly to the development of dementia prevention measures in Japan.

Clinical trial registration number: UMIN000041938

1. Introduction

Dementia caused by neurodegenerative diseases, such as Alzheimer's disease, is characterised by a decline in cognitive function and the abilities necessary to perform activities of daily living (ADL). The number of people living with dementia increases worldwide every year. Dementia worsens the quality of life (QOL) of patients and their families and increases the burden on society in terms of healthcare costs (Alzheimer's Disease International et al., 2015).

Just as the development of medications to treat Alzheimer's disease is increasingly targeting people in the early or prodromal stages (Cummings et al., 2019), non-pharmacological interventions to delay the onset and progression of dementia must be used as early as possible. Recent observational studies have shown various risk factors for the development of dementia (Silva et al., 2019). Although exercise, cognitive training, and lifestyle counselling may help reduce the risk of

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dementia, the effects of any single intervention are unclear or limited (Colcombe & Kramer, 2003; Park et al., 2019; Willis et al., 2006). Therefore, in recent years, the effectiveness of multi-domain interventions in preventing dementia has received much focus, and several randomised controlled trials (RCTs) have been reported. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first large RCT of a multidisciplinary intervention (nutritional counselling, physical exercise, cognitive training, vascular risk monitoring, and social stimulation) that demonstrated efficacy in reducing cognitive decline in older adults at risk for developing dementia (Ngandu et al., 2015). Four other large RCTs, the Taiwan Health Promotion Intervention Study for Elders (THISCE; Chen et al., 2020), the Taiwan Integrated Geriatric Care (TIGER; Lee et al., 2021), the Multidomain Alzheimer Preventive Trial (MAPT; Andrieu et al., 2017) and the Prevention of Dementia by Intensive Vascular Care (preDIVA; Moll van Charante et al., 2016) have also been conducted. Of these, the THISCE trial and the TIGER trial showed an improvement in cognitive function with multi-domain intervention, while the primary outcomes of the MAPT trial and preDIVA trial were not significant. Differences may influence this inconsistency in the results of multiple studies in target populations, intervention methodologies, and outcome measures across studies (Kivipelto et al., 2020).

Based on these results, studies have been conducted worldwide to test the effectiveness of multi-domain interventions. In 2017, the World-Wide FINGERS (WW-FINGERS) network was launched at the Alzheimer's Association International Conference in London, based on the FINGER methodology. Over 40 countries currently participate in the WW-FINGERS network, which aims to accumulate data and generalise strategies to prevent cognitive impairment and dementia by promoting new clinical research practices (Kivipelto et al., 2020). In Japan, the Japan-Multimodal Intervention Trial for Prevention of Dementia (J-MINT) began in 2019 and is included in the WW-FINGERS network (Sugimoto et al., 2021). The trial consisted of the main study led by the National Centre for Geriatrics and Gerontology (NCGG) and extension studies with a similar intervention protocol to increase generalisability. The main study's participants are those with objective cognitive decline, whereas the extension studies' participants are at a lower risk of dementia than the main study's participants. Extension studies will be conducted to test the effectiveness of earlier dementia prevention interventions tailored to local conditions.

The J-MINT PRIME Tamba study is an RCT that uses a protocol similar to the J-MINT study and is an extension study being conducted in Tamba City by Kobe University. Tamba City is in the north-eastern region of Hyogo Prefecture, Japan, with approximately 62,000 residents and an ageing population rate of 35%, as of April 2022. The region is characterised by a relatively high ageing population and a high rate of people at risk for vascular diseases, such as hypertension and diabetes. Thus, the Tamba City Office is taking a progressive and proactive approach to medical and health care and has signed a basic agreement with Kobe University for a longitudinal study on dementia prevention and extending healthy life expectancy from 1 May 2019, before the start of this study.

This study aims to conduct an RCT to examine the efficacy of a multi-domain dementia prevention programme, which consists of lifestyle-related disease management, physical exercise, nutrition counselling, and cognitive training on improving or maintaining cognitive function or reducing cognitive decline in older people at risk for dementia.

2. Methods

2.1. Study design (see Fig. 1)

The J-MINT Prime Tamba study is designed as an RCT with 78 interventions, delivered as one intervention per week. The intervention group will receive interventions comprising four domains: lifestyle-related disease management, physical exercise, nutritional counselling, and cognitive training. The control group will receive pamphlets on

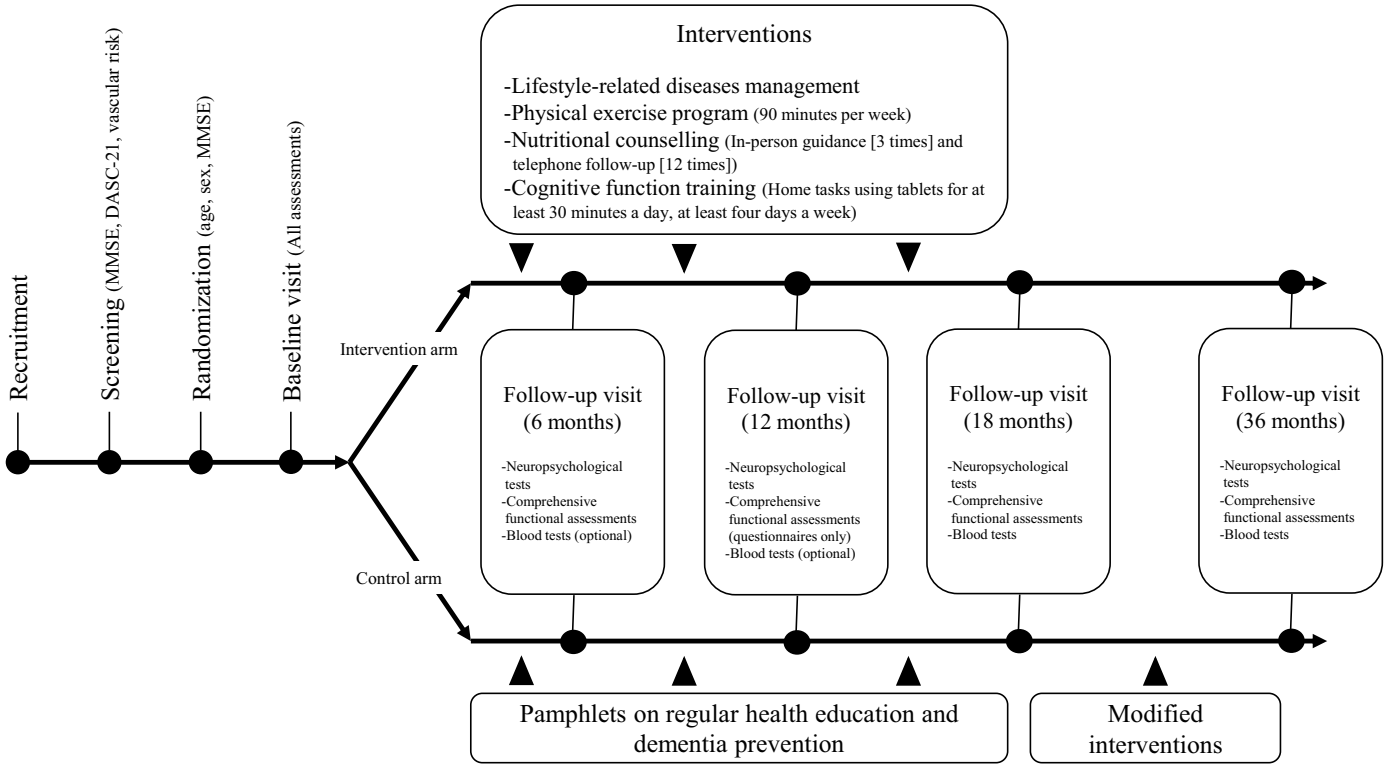

Fig. 1. Japan-multimodal intervention trial for prevention of dementia PRIME Tamba (J-MINT PRIME Tamba) protocol.
MMSE, Mini-Mental State Examination; DASC-21, Dementia Assessment Sheet in Community based Integrated Care System-21 items.

regular health education and dementia prevention, and after the completion of the trial, those who wish to participate can take part in the programme for the same length of time as the intervention group, with modified content. The participants in both groups will be evaluated at baseline and again at 6, 12, 18, and 36 months.

2.2. Ethics committee review and approval

All research plans are reviewed and approved by the Kobe University Ethics Committee for Health Sciences, and study information is registered in the University hospital Medical Information Network-Clinical Trials Registry system and published on the web (clinical trial registry number: UMIN000041938). All participants will be fully informed about the study, and their written consent to participate will be obtained after they fully understand the benefits and potential risks of participating in the study.

2.3. Eligibility criteria (inclusion and exclusion criteria)

Participants in the trial must meet the following criteria:

1 They live in Tamba and are between 65 and 85 years old at enrolment.
2 Their total score on the Dementia Assessment Sheet in Community-based Integrated Care System-21 items (DASC-21; Awata et al., 2016), which assesses cognitive decline and ADL decline simultaneously, is between 22 and 30 points.
3 They have one of the following vascular risk factors: receiving treatment for hypertension, systolic blood pressure $\geq$ 140mmHg or diastolic blood pressure $\geq$ 85mmHg, receiving treatment for diabetes, or HbA1c $\geq$ 6.0%.

Participants will be excluded according to the following criteria:

1 Owing to functional impairment, including bone or joint disease, renal failure, unstable ischemic heart disease, and cardiopulmonary conditions, they need to restrict any physical exercise or diet.
2 They have been diagnosed with dementia.
3 They have a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score below 24.
4 They cannot speak Japanese.
5 They cannot undergo cognitive tests due to severe vision and/or hearing impairment.
6 Under the Japanese Long-Term Care (LTC) Insurance Act, they have been certified as requiring LTC Level 1 or higher (need more care). LTC Level 1 refers to those who require minimal care for basic ADL such as bathing and elimination.
7 They have been deemed unsuitable for the trial by a primary care physician or family doctor for reasons such as a risk of worsening physical illness.

2.4. Recruitment and enrolment

Among those who received a specific health check-up for people aged 65 years or older conducted by Tamba City between April 2019 and March 2020, Kobe University administered the DASC-21 to 2280 people as part of another research project. Those who meet inclusion criteria (2) and (3) above will be recruited by mail—these people did not receive any intervention in the earlier study. Additionally, participants will also be recruited using newspaper inserts and local press releases.

Those interested in participating in the study will be invited to a brief session, and the contents will be explained orally and in writing. After the explanation, those who wish to participate in the study will be screened using the MMSE and DASC-21. They will also be screened for vascular risk to confirm that they meet the eligibility criteria. Those who meet the eligibility criteria will be given further detailed explanations orally and in writing, and written consent will be obtained after the participant fully understands the benefits and potential risks of taking part in this study.

2.5. Randomisation and blinding

Based on age, sex, and MMSE score information obtained during the screening, participants will be randomly assigned to one of two groups in a 1:1 ratio using a dynamic allocation method with stratification factors. The stratification criteria are as follows: (1) age: 65–74 years or 75–85 years, (2) sex: female or male, and (3) MMSE score: 24–27 or 28–30. The researchers will register participants in the electronic data capture (EDC) system, and the external organisation that runs the EDC system will perform dynamic allocation using an algorithm that blinds the researchers and participants.

Naturally, all participants will know their group allocation. All assessors will be blinded; however, researchers and administrative staff who can log in to the EDC system have the possibility of knowing the allocation results. Additionally, one researcher and three administrative staff may be present at the intervention site; however, they will ensure that there is no co-intervention.

2.6. Intervention procedures

The intervention group will receive multi-domain interventions, including lifestyle-related disease management, physical exercise (including cognitive training elements such as dual-task exercises), nutritional counselling, and cognitive training. Lifestyle-related management and physical exercise programmes will be carried out at the intervention site once a week. Nutritional counselling by visiting or calling the participants at their homes will be provided by Sompo Health Support, Inc., which has a nationwide network of public health nurses, nutritionists, and other professionals in Japan and provides health guidance to numerous companies. Cognitive training will be carried out by the participants themselves at home using a tablet.

2.6.1. Management of lifestyle-related diseases

According to the critical practice guidelines, participants with diabetes, hypertension, or dyslipidaemia will be managed by the supervisors, who are health professionals such as public health nurses and nutritionists. To manage each disease, the following will be used: the Treatment Guideline for Elderly Patients with Diabetes Mellitus by the Japan Diabetes Society & Japan Geriatrics Society (2017), Japanese Society of Hypertension Guidelines for the Management of Hypertension (Umemura et al., 2019), and the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (Kinoshita et al., 2018).

2.6.2. Physical exercise programme

Participants will be provided with an exercise programme consisting of aerobic exercise, dual-task exercise, strength training, and group meetings for 90 min per session, once weekly for 18 months. The programme instructors are qualified health professionals, such as physical therapists.

To ensure that the exercise programme is conducted safely, the practitioners will conduct medical checks, including blood pressure and pulse rate measurements and a medical interview before participants begin exercising. If any of the following criteria are met, the participant's intervention for that day will not be implemented: resting systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 100 mmHg, resting pulse rate greater than 100 beats/min or less than 50 beats/min, unusual pulse irregularity, or worsening of chronic symptoms, such as joint pain.

The exercise programme will be structured as described in the following: (1) Aerobic exercise will include aerobics and step exercises, which will be performed for approximately 30 min under a

practitioner's guidance. The participants' pulse rate will determine the exercise intensity, which will gradually be increased from 40% to 80%. (2) Dual-task exercise, which is a programme combining exercise and cognitive tasks, will be performed for approximately 30 min. (3) Strength training will be performed under a practitioner's guidance, including weight-bearing muscle-strengthening exercises in a sitting or standing position for approximately 30 min. (4) Group meetings will include a five-minute lecture on health behaviour from a practitioner and a discussion session with the participants, lasting approximately 30 min in total. During the exchange of opinions, participants will be asked to review their behaviour and record their daily activities, and all participants will encourage the subject's activities. Programmes (3) and (4) will not be held every time but will alternate by week.

2.6.3. Nutritional counselling

Participants will be provided with nutritional counselling by health counsellors, such as public health nurses, nurses, and dietitians, through face-to-face interviews during the first, seventh, and thirteenth months and telephone follow-ups every five weeks after the visits. The nutrition counselling programme will consist of dietary assessment, behavioural goal-setting, intake of foods that are good for dementia prevention, such as fish, chicken, beans/soybean products, vegetables/seaweed, seasonal foods, and colourful and diverse food combinations, and oral care guidance for oral frailty.

In the dietary assessment, the counsellor will listen to the participants' daily routine, such as sleeping hours, time and amount of meals, dietary diversity, and current and previous medical history. Based on this information and results such as height and weight and biochemical data, the counsellor will identify the participant's problems with diet and eating habits. In addition to providing guidelines on the problems identified, the counsellor will propose behavioural goals that match the participant's preferences.

During the 7- or 13-month interview, participants will receive guidance on foods and nutrients that have been shown to be effective in preventing dementia. In addition to the above, health counsellors will add food and nutrient intake according to the participant's preferences as a behavioural goal.

Finally, participants will receive guidance on oral frailty. They will be assessed based on their number of remaining teeth and answers to a questionnaire and will receive a leaflet with instructions for oral hygiene and oral exercise. This assessment and intervention will be applied to all participants in the intervention group.

2.6.4. Cognitive function training

Participants will receive cognitive function training using a tablet with the software program BrainHQ (Posit Science Corp., CA, USA) installed. The BrainHQ version that will be used in this study is operated by Nestle Japan, Ltd. and provides training in information processing, attention, memory, and visuospatial cognition. Participants will engage in cognitive function training lasting at least 30 min per day for four or more days per week, following an interval style, with practice and rest periods every three months. Every three months, they will receive feedback on changes in their task level over time.

Some participants are expected to drop out of the cognitive training due to difficulties in operating the tablet; therefore, support will be provided at the start of the programme by explaining how to operate the tablet, as well as by setting up a free consultation service during the study period.

2.6.5. Infection control and intervention during the COVID-19 pandemic

Measures will be taken to prevent COVID-19 infection, such as limiting long-distance travel, maintaining social distance, and avoiding the '3Cs' (i.e. closed spaces, crowded places, and close-contact settings). When the Japanese government declares a state of emergency due to the COVID-19 pandemic, interventions involving direct contact, such as physical exercise and face-to-face nutrition counselling, may be switched to online interventions.

2.7. Assessments

All participants will complete neuropsychological testing at baseline and at 6, 12, 18, and 36 months, as well as a comprehensive functional assessment at baseline and at 6, 18, and 36 months. Additionally, participants will be asked to complete questionnaires on health behaviours and attitudes towards intervention studies at baseline and at 6, 18, and 36 months. Participants will also receive blood tests at baseline and at 6, 18, and 36 months, as well as the Cogstate Brief Battery (Cogstate Ltd., USA and Australia; Fredrickson et al., 2010) and Cognitive function balancer (Total Brain Care Co. Ltd., Hyogo, Japan; Ichii et al., 2020) as needed. Table 1 summarises the assessments.

2.7.1. Neuropsychological tests

Participants will undergo neuropsychological tests, including the MMSE, which is an assessment of overall cognitive functioning, as well as tests that involve the following three cognitive function domains: memory (the free and cued selective reminding test [FCSRT]; Grober & Buschke, 1987; Japanese version and logical memory I and II subsets of the Wechsler Memory Scale-Revised [WMS-R]; Powel, 1988), attention (digit span test of the Wechsler Adult Intelligence Scale [WAIS-III]; Wechsler, 1955), executive function/processing speed (digit symbol substitution test [DSST] subset of the WAIS-III, trail making test [TMT]; Lezak, 2004, and letter word fluency test). Sessions are expected to take approximately one hour each and will be conducted at baseline and at 6, 12, 18, and 36 months.

The assessors will be limited to those with medical qualifications,

Table 1
Summary of the assessments.

	Periods	Contents
Neuropsychological tests	at baseline and at 6, 12, 18, and 36 months	MMSE; FCSRT; logical memory; digit span; DSST; TMT; letter word fluency test
Questionnaires	at baseline and at 6, 12, 18, and 36 months	basic/instrumental ADLs; frailty; dietary diversity; nutritional status; appetite; depressive symptoms; falls; social isolation; health-related QOL; sleep quality; social participation; hearing loss; subjective fatigue; visual function; subjective cognitive decline
Physical measurements	at baseline and at 6, 18, and 36 months	height; body weight; body mass index; body composition; calf circumference; blood pressure; pulse rate
Physical performance	at baseline and at 6, 18, and 36 months	handgrip strength; walking speed; lower extremity muscular strength; lung function
Blood tests	at baseline and at 6, 18, and 36 months	glucose, insulin, haemoglobin A1c, glycoalbumin, total protein, albumin, white blood cells, red blood cells, haemoglobin, haematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total cholesterol, high-density lipoprotein-cholesterol, triglyceride, creatinine, estimated glomerular filtration rate, blood urea nitrogen, sodium, potassium, chloride, calcium, phosphorus, 25-hydroxy vitamin D, glucagon-like peptide-1, and apolipoprotein E (APOE) phenotype*

* Apolipoprotein E (APOE) phenotype only test at baseline.
MMSE, mini-mental state examination; FCSRT, free and cued selective reminding test; DSST, digit symbol substitution test; TMT, trail making test.

such as physical therapists, occupational therapists, nurses, speech therapists, and psychologists, and they will be required to watch a four-hour video training session and undergo a two-hour online training session. For the logical memory section of the WMS-R, responses will be recorded with a voice recorder, and two psychologists affiliated with the NCGG will score all participants to minimise inter-rater differences in scoring.

2.7.2. Comprehensive functional assessment

Comprehensive functional assessments will include self-report questionnaires, physical measurements, and physical function tests.

2.7.2.1. Questionnaires. Participants will be assessed for the following:

1. Basic ADLs: basic self-care abilities, such as feeding, transferring from a bed to a chair, bathing, bowel control, and bladder control, ranging from 0 (complete dependence) to 100 (complete independence), assessed using the Barthel Index (Mahoney & Barthel, 1965),
2. Instrumental ADLs: comprises eight items, such as using the telephone, shopping, and handling medications, ranging from 0 (low function) to 8 (high function), assessed using the Lawton Index (Lawton & Brody, 1969).
3. Frailty: weight loss, decreased physical activity, decreased vitality, and social frailty, assessed via a questionnaire.
4. Dietary diversity: frequency of consuming 14 food items in the past week, assessed using the 11-item Food Diversity Score Kyoto (Kimura et al., 2009).
5. Nutritional status: comprises six questions, scores ranging from 0 to 14, with a higher score indicating better nutritional status, assessed using the Mini Nutritional Assessment-Short Form (Rubenstein et al., 2001).
6. Appetite: assessed using the Comprehensive Nutritional Appetite Questionnaire (Wilson et al., 2005).
7. Depressive symptoms: ranging between 0 and 15, with a higher score indicating a higher level of depressive symptoms, assessed using the 15-item Geriatric Depression Scale (GDS-15; Sugishita et al., 2017). This form of the GDS comprises 15 self-report yes-or-no questions that were derived from the GDS-30.
8. Falls: history of falls within the past 12 months and fall risk, assessed using a questionnaire.
9. Social isolation: comprises six questions, scores ranging from 0 to 30, with a higher score indicating a better social network; a score below 12 is considered an indicator of social isolation, assessed using the Lubben Social Network Scale-short version (Lubben et al., 2006), which measures social network size according to the number and frequency of contacts with friends and family and social support.
10. Health-related QOL: comprises five dimensions—mobility, self-care, pain/discomfort, usual activities, and anxiety/depression—assessed using the EuroQoL 5-Dimension 5-Level (Kunz, 2010), which measures general QOL in mobility, self-care, daily living, pain/discomfort, and anxiety/depression. For example, it asks participants if they have difficulty walking. For each question, participants will select the most suitable option, according to their health status, among five levels: 'no difficulty', 'a little difficulty', 'moderate difficulty', 'severe difficulty', and 'unable to proceed/have very serious difficulty'.
11. Sleep quality: comprises subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, with a higher score indicating poor sleep quality, assessed using the Pittsburgh Sleep Quality Index (Buysse et al., 1989).
12. Social participation: participation in community groups and associations, assessed using a questionnaire.
13. Hearing loss: assessed using the Hearing Handicap Inventory for the Elderly (Ventry & Weinstein, 1982).
14. Subjective fatigue: assessed using the Checklist Individual Strength (Vercoulen et al., 1994).
15. Visual function and vision-related QOL: assessed using the 25-item National Eye Institute Visual Function Questionnaire (Mangione et al., 2001).
16. Subjective cognitive decline: subjective assessment of decline in daily functioning associated with cognitive decline, assessed using the Cognitive Function Instrument-Japanese version (Amariglio et al., 2015; Osaki et al., 2021).

2.7.2.2. Physical measurements. Data on participants' height, body weight, body mass index, body composition, calf circumference, blood pressure, and pulse rate will be collected. The bioelectrical impedance method will be followed to evaluate skeletal muscles using a body composition analyser (Inbody 770, Inbody Japan, Tokyo, Japan), and the skeletal muscle mass index will be calculated as skeletal muscle mass in the limbs. Phase angle, body fat mass, and the fat-free mass index will also be included in the body composition evaluation. Measurements will be taken for all participants except those wearing a cardiac pacemaker.

2.7.2.3. Physical performance. Indicators of physical performance include handgrip strength, walking speed, lower extremity muscular strength, and lung function. Handgrip strength (kg) will be measured using a Smedley hand dynamometer (Grip-D Smedley-T.K.K.5401, Takei Scientific Instruments Ltd., Niigata, Japan) with the participant in a standing position, with two trials from each hand alternately. The maximum and left-right mean values of the available scales will be used for the analysis.

Walking speed will be measured on a 2.4 m walking path, which is commonly used in normal walking speed tests. At the time of measurement, a 1.0 m acceleration and deceleration path will be set up. Participants will be instructed to walk at their normal pace from a standstill to the end of the deceleration path, and the time between passing the 1.0 m acceleration path and the 2.4 m point will be measured with a digital stopwatch. This procedure will be repeated twice to calculate the walking speed (m/s; Toots et al., 2021). If participants use a normal walking aid, the measurement will be taken with the aid in place and noted in the remarks column.

The five times sit-to-stand (5STS) test will be performed using a standard chair height (43 cm), with participants instructed to not use their arms. Participants will receive the following instructions: 'stand up from the chair, then sit down as quickly as possible for five repetitions, and do not use your hands during the test'. The assessor will ensure that participants stand up completely (i.e. full extension) and sit down (i.e. touch the chair) between each repetition. One trial of the 5STS test will be performed, with the time taken to complete the 5STS recorded with a stopwatch. The stopwatch recording will start and end with the participant sitting with their back against the chair. Trials will be repeated if participants use their arms, do not stand up completely, or do not sit down between repetitions (Mentiplay et al., 2020).

Lung function will be measured using a spirometer (AS-407, Minato Medical Science Ltd., Japan), calibrated daily according to the 2014 ATS guidelines (Redlich et al., 2014). Forced expiratory volume in one second (FEV1), percent-of-predicted FEV1 (FEV1%), forced vital capacity (FVC), and FEV1/FVC will be recorded.

Maximum expiratory pressure (PImax) and maximum expiratory pressure (PEmax) scores will be measured as indices of respiratory muscle function using a respiratory muscle strength measuring device (IOP-01, Kobata Instrument Manufacturing Ltd, Osaka, Japan). Measurements will be made according to the American Thoracic Society European Respiratory Society Statement on Respiratory Muscle Testing, and each participant's score will be measured at least thrice. Measurements taken during coughing, leakage, instrument obstruction, or other

disorders will be excluded from the analysis. Three measurements with less than 20% variation will be included in the calculation and recorded as the minimum PImax and maximum PEmax values (American Thoracic Society/European Respiratory Society, 2002).

2.7.2.4. Other measurements. Physical activity and sleep quality will be monitored using a wristwatch device (Inspire HR, Fitbit Inc., CA, USA). Variability in reaction time will be measured by performing 120 trials of a choice reaction task, assessed using E-Prime software and a Chronos device (Psychology Software Tools Inc., PA, USA).

2.7.3. Blood tests

Blood tests will be performed at baseline and at 18 and 36 months during the study. The following will be evaluated: glucose, insulin, haemoglobin A1c, glycoalbumin, total protein, albumin, white blood cells, red blood cells, haemoglobin, haematocrit, platelets, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total cholesterol, high-density lipoprotein-cholesterol, triglyceride, creatinine, estimated glomerular filtration rate, blood urea nitrogen, sodium, potassium, chloride, calcium, phosphorus, 25-hydroxy vitamin D, glucagon-like peptide-1, and apolipoprotein E (APOE) phenotype.

2.8. Statistical analysis

2.8.1. Analysis of the primary outcome

The primary outcome measure is the change in cognitive function from baseline to 18 months in a global composite score. The composite score will be calculated by averaging the Z-scores of each neuropsychological test (i.e. MMSE, FCSRT, logical memory, digit span, DSST, TMT, and letter word fluency test). The mean and standard deviation of each neuropsychological test score at baseline will be used to standardise the Z-score.

The change in composite scores between baseline and 18 months will be calculated for each participant. Between-group comparisons will be performed by conducting a t-test and the difference in the mean change in composite score between groups and its 95% confidence interval. If necessary, an adjusted analysis will also be performed using a linear model and a longitudinal data analysis that considers the data at 6 and 12 months.

2.8.2. Analysis of secondary outcomes

Secondary outcome measures include a change in cognitive function from baseline to 6, 12, and 36 months in the global composite score; change in each neuropsychological test from baseline to 6, 12, 18, and 36 months; change in blood test values from baseline to 6, 12, 18, and 36 months; change in ADL function and frailty from baseline to 6, 18, and 36 months; change in reaction time from baseline to 18 months; and change in cognitive function screening from baseline to 18 months.

For continuous values, groups will be compared by conducting a t-test and calculating the difference in the mean change in each value between groups and their 95% confidence interval for the primary outcome. The incidence rates between groups will be compared by conducting a chi-square test or Fisher's exact test, with adjustment analysis and longitudinal data analysis if necessary. The Clopper–Parson method will be used to calculate confidence intervals for incidence rates.

The frequency and rate of adverse events will also be aggregated, and 95% confidence intervals will be calculated using the Clopper–Pearson method. For demographic characteristics and other items, the distribution of each variable will be compared between groups by conducting a t-test and chi-squared test or Fisher's exact test, respectively, with means and standard deviations obtained for continuous variables and proportions as indicators for categorical variables. All tests are two-tailed, with a significance level of 5%.

2.8.3. Sample size

The J-MINT study was the first large-scale RCT in Japan aimed at preventing cognitive decline, and no previous studies used each neuropsychological test's composite score, which is the study's primary outcome measure. A meta-analysis of RCTs using cognitive-based training as the intervention method showed that overall cognitive function improved in the intervention group, with a Hedges' *g* of 0.419 (Chiu et al., 2017). The sample size required for a two-tailed t-test with a risk rate of 5%, a power of 80%, and an allocation ratio of 1:1 was 182 participants. A similar effect size was assumed in the present study. If the dropout rate from baseline to 18 months was assumed to be approximately 10%, approximately 200 participants would need to be enrolled.

2.9. Data management and data security

2.9.1. Adverse events and serious adverse events

To evaluate the safety of the intervention, all adverse events (AEs) and serious AEs will be monitored during the trial. The information that will be collected about AEs will include their date of onset, severity, associated treatment, consequences, and causation. Serious AEs will be reported to the principal investigator, the IRB, and the co-investigators immediately (Sugimoto et al., 2021).

2.9.2. Data collection forms and data monitoring

Trained research staff will measure all the variables, and most of the measured outcome data will be collected in hard copy forms. Then, assessors will enter these data by using an electronic data capture (EDC) system for data collection. All hard copy forms will be retained as backups as required.

On-site monitoring will be conducted to ensure that participant rights are protected, the reported data are accurate, and the trial conduct is compliant with the currently approved protocol. The monitor will ensure that (1) written informed consent is obtained from all participants before their participation in the trial, (2) primary outcome data reported in the EDC are complete and accurate, (3) all AEs and serious AEs are reported appropriately, (4) the study data are consistent with source documents, and (5) the study is compliant with exercise and nutrition intervention manuals (Sugimoto et al., 2021).

3. Discussion

The J-MINT PRIME Tamba trial will validate a multi-domain intervention's effectiveness and a comprehensive assessment including cognitive function, physical function, and blood tests in preventing cognitive decline in community-dwelling older adults with vascular risk factors. The results of this trial are expected to demonstrate the multidomain intervention's effectiveness, clarify the mechanisms of cognitive function improvement and deterioration, and build evidence for dementia prevention.

The J-MINT PRIME Tamba trial is related to the J-MINT trial (Sugimoto et al., 2021). However, the settings differ in several respects (see Table 2), characterised by the participant selection criteria and the implementers of the physical exercise intervention. In the J-MINT trial, sports club instructors provided interventions for those with slightly lower scores on the National Centre for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013; Shimada et al., 2017) and a computer-based cognitive function test. In contrast, in the J-MINT PRIME Tamba trial, physical therapists and occupational therapists in the same prefecture as Tamba will intervene, with individuals who have mild subjective cognitive decline and are at vascular risk. These differences exist because the J-MINT's overall goal was strongly geared towards the realisation of social implementation, and research results were used in line with local conditions.

The J-MINT PRIME Tamba trial is being conducted with the strong cooperation of Tamba City and will continue to be developed into a dementia measure for Tamba City after the trial is completed. Further,

Table 2
Similarities and differences between the two J-MINT study protocols.

	J-MINT PRIME Tamba	J-MINT
Target sample size	**200**	500
Recruitment area	**Rural**	Urban
Key recruitment targets	**Health check-up recipients**	Hospital visitors/ community cohort
Key inclusion criteria	**Their total score on the DASC-21 is between 22 and 30 points. They have one of the following vascular risks: being treated for hypertension, systolic blood pressure≥140mmHg or diastolic blood pressure≥85mmHg, being treated for diabetes, HbA1c≥6.0%.**	They have age-adjusted decline at least 1.0 SD from the reference threshold in any cognitive domains measured by using the NCGG-FAT.
Implementers of the physical exercise	**Physical therapists and occupational therapists**	Sports club instructors
Assessments/ Interventions	**Identical**	
Primary outcomes	**Identical**	
Research institutions	**Single-centre (Kobe University)**	Multi-centre (NCGG and four other centres)
UMIN-CTR	**UMIN000041938**	UMIN000038671

DASC-21, the Dementia Assessment Sheet in Community based Integrated Care System-21 items; NCGG-FAT, the National Centre for Geriatrics and Gerontology Functional Assessment Tool; UMIN-CTR, the University hospital Medical Information Network-Clinical Trials Registry.

the J-MINT PRIME Kanagawa trial (UMIN000041887) will be conducted in Kanagawa Prefecture with a protocol similar to that for Tamba. All J-MINT trials will assess outcomes such as cognitive function using the same methods, and a combined data analysis of each is planned. These results are believed to contribute to developing a general framework for providing dementia prevention services to a broader population.

CRediT authorship contribution statement

Ryoko Kumagai: Conceptualization, Methodology, Investigation, Writing – original draft. **Tohmi Osaki:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Yutaro Oki:** Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration. **Shunsuke Murata:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Kazuaki Uchida:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Haruhi Encho:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Rei Ono:** Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration. **Hisatomo Kowa:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

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