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SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through Multidomain interventions via facE-to-facE and video communication plaTforms in mild cognitive impairment (SUPERBRAIN-MEET): Protocol for a Multicenter Randomized Controlled Trial

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ABSTRACT

Background and Purpose: The SoUth Korea study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention (SUPERBRAIN) proved the feasibility of multidomain intervention for elderly people. One-quarter of the Korean population over 65 years of age has mild cognitive impairment (MCI). Digital health interventions may be cost-effective and have fewer spatial constraints. We aim to examine the efficacy of a multidomain intervention through both face-to-face interactions and video communication platforms using a tablet personal computer (PC) application in MCI.
Methods: Three hundred participants aged 60–85 years, with MCI and at least one modifiable dementia risk factor, will be recruited from 17 centers and randomly assigned in a 1:1 ratio to the multidomain intervention and the waiting-list control groups. Participants will receive the 24-week intervention through the tablet PC SUPERBRAIN application, which encompasses the following five elements: managing metabolic and vascular risk factors, cognitive training,

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Conflict of Interest
CHH received research support from Eisai Korea Inc. SYM, CHH, JHJ, YKP, HRN, and SHC are shareholders of Rowan Inc. JHJ and SHC consult for PeopleBio Co. Ltd. JJ reported being an employee of Rowan Inc. MC reported being the head of Exercowork. The remaining authors declare that the research was conducted in the absence of any commercial

physical exercise, nutritional guidance, and boosting motivation. Participants will attend the interventions at a facility every 1–2 weeks. They will also engage in one or two self-administered cognitive training sessions utilizing the tablet PC application at home each week. They will participate in twice or thrice weekly online exercise sessions at home via the ZOOM platform. The primary outcome will be the change in the total scale index score of the Repeatable Battery for the Assessment of Neuropsychological Status from baseline to study end.
Conclusions: This study will inform the effectiveness of a comprehensive multidomain intervention utilizing digital technologies in MCI.

Trial Registration: ClinicalTrials.gov Identifier: NCT05023057

Keywords: Randomized Controlled Trial; Dementia; Cognitive Impairment; Secondary Prevention; Lifestyle

INTRODUCTION

Approximately 50 million individuals globally are affected by dementia, and this figure is projected to increase to 152 million by the year 2050.[1] A promising study recently revealed that there are 12 modifiable risk factors that can be managed to potentially reduce dementia prevalence by 40%.[1] These risk factors include poor education in early life (age <45 years), hypertension, obesity, hearing impairment, excessive alcohol consumption, head injury at 45–65 years, depression, smoking, physical inactivity, diabetes, air pollution, and infrequent social contact in later life (age >65 years). Meanwhile, in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial, a lifestyle intervention addressing multiple domains—including the promotion of a healthy diet, engaging in physical exercise, cognitive training, and managing metabolic and vascular risk factors—led to a significant enhancement in cognition compared to a control group.[2] The World Health Organization has emphasized the need for additional research investigating the effectiveness of multidomain interventions that have been customized to distinct geographic and cultural settings.[3] The creation of the World-Wide FINGERS (WW-FINGERS) network was intended to assist clinical trials focused on preventing dementia through multidomain interventions and facilitating the exchange of experiences and data.[4]

The SoUth Korean study to PrEvent cognitive impaiRment and protect BRAIN health through lifestyle intervention (SUPERBRAIN) in at-risk elderly people is one study affiliated with the WW-FINGERS network.[4,5] The previous SUPERBRAIN trial evaluated the feasibility of home-based multidomain intervention (HMI) and facility-based multidomain intervention (FMI) programs targeted toward older Korean people.[6] The adherence rates were approximately 95% in both the HMI and FMI groups. The retention rates of the HMI and FMI groups were 96% and 88%, respectively. The total scale index score of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) showed a significant improvement in each of the HMI and FMI groups when compared to the control group. Ultimately, the results of that study showed that HMI and FMI are both feasible and have indicators of efficacy. The participants in the FMI group engaged in all intervention programs at a facility thrice weekly. The participants in HMI group engaged in some programs at a facility once every one to two weeks whereas they engaged in other programs at home. The HMI program can be useful when outdoor activities are restricted due to air pollution or the spread of infectious diseases such as coronavirus disease 2019 (COVID-19). However, programs that are completed at home require close monitoring.

Table 4. Contents of nutrition sessions

Time	Contents	Tool
Week 1	Nutrition program orientation	App) Nutrition education video 1
Week 2	Nutrition assessment (dietary habits, food intake, etc.)	Phone) Counselling 1
Week 3	MIND diet education	App) Nutrition education video 2
Week 4	Nutrition intervention: tailored solution 1	Phone) Counselling 2
Week 5	Vegetables-Fish-Nuts-Fruits-Olive oils are the best!	App) Nutrition education video 3
Week 7	Recommended nutrient intake of food groups for each day: vegetables (fibers) and carbohydrates	App) Nutrition education video 4
Week 8	Nutrition intervention: tailored solution 2	Phone) Counselling 3
Week 10	Recommended nutrient intake of food groups for each day: proteins	App) Nutrition education video 5
Week 12	Cooking class: application of MIND diet	App) Nutrition education video 6
Week 14	What should you drink when you're thirsty?	App) Nutrition education video 7
Week 16	How to eat: low salt, low sugar!	App) Nutrition education video 8
Week 18	What are healthy snacks	App) Nutrition education video 9
Week 20	Food for healthy bones: the best calcium-rich foods	App) Nutrition education video 10
Week 22	The importance of health care in old age (age-related diseases)	App) Nutrition education video 11
Week 24	Let's promise to practice what we learned	App) Nutrition education video 12

MIND diet: The Mediterranean-Dietary Approaches to Stop Hypertension Diet Intervention for Neurodegenerative Delay diet, App: application.

The nutritional intervention will include three individual phone consultations (each lasting 30 minutes) with a research dietitian and additional viewing of a nutrition education video created by a nutrition professor on the tablet PC when visiting the facility once every two weeks. The individual phone consultations will be held during the 2nd, 4th, and 8th weeks, and they will include tailoring to the participant's daily dietary needs and educating them on customized diets to manage individual vascular risk factors. Nutrition education videos will provide dietary education, practical exercises for facilitating eating changes, and advice on how to cook meals with recommended ingredients through cooking lessons (**Table 4**). As recommended by the Mediterranean-Dietary Approaches to Stop Hypertension diet Intervention for Neurodegenerative Delay (MIND) diet,[23] participants will be advised to consume a diet of at least three servings of whole grains each day; six or more dark green vegetable serving each week; one or more servings of other vegetables each day; five or more servings of nuts each week; four or more servings of beans or legumes each week; berries and poultry at least twice a week; and fish at least once a week. They will also be advised to use olive oil as cooking oil and limit themselves to no more than a glass of wine each day for alcohol drinkers; less than once a week for cheese, fried food, and fast food; less than five servings a week for pastries and sweets; and less than four servings per week for red meat and products. Participants will find motivation to complete the MIND diet checklist weekly using the tablet PC.

Motivational enhancement will comprise four group counseling sessions, each lasting 50 minutes, which will be led by a study coordinator at weeks 1, 2, 12, and 24. The motivational enhancement program will aim to instigate, sustain, and reinforce motivation, thereby serving as a psychological resource to support the continuity of dementia prevention activities.

The participants' motivation and self-efficacy levels will be evaluated during each motivational enhancement session. The details of the motivational enhancement program are presented in **Table 5**. Moreover, the family coach program will allow a family member to reinforce a participant's motivation. Participants will receive video messages from their families cheering them on and opportunities for self-assessments of their achievements in the form of pop-up notifications every week before the tablet-based cognitive intervention.

Table 5. Contents of motivation enhancement sessions

Time	Contents
Week 1	Providing education on the importance of lifestyle changes in preventing dementia, along with watching a video depicting an elderly individual who has suffered dementia due to not engaging in dementia prevention activities.
Week 2	Introducing success stories related to dementia prevention activities. Sharing both proactive endeavors and ambivalent feelings regarding engagement in dementia prevention activities with one another.
Week 12	Sharing efforts to take part in dementia prevention activities with one another. Sharing what participants want their older age to look like.
Week 24	Sharing success experiences in dementia prevention activities and experiencing a sense of pride. Viewing a video illustrating a vibrant and healthy old age. Culminating in a graduation ceremony.

Control condition

At baseline, participants in the control group will meet a study doctor, whom may prescribe them medication if necessary, and they will be given a booklet containing lifestyle guidelines for dementia prevention. Participants will also be notified that they will be permitted to participate in the multidomain intervention program after the conclusion of this study while continuing to receive their usual care.

Outcome measures

The primary outcome will be the change in the RBANS total scale index score with the normative data of Korean adults throughout the study, measured from baseline to study end.[24] The RBANS comprises 12 subtests and assesses five cognitive domains: attention, language, visuospatial/constructional abilities, immediate memory, and delayed memory. The index score for each cognitive domain (range, 40–160) is individually adjusted for different age groups to achieve a scaled score mean of 100 with a standard deviation of 15.[25] The total scale index score (range, 40–160) is derived from the sum of five index scores, which also has a normal mean of 100 and a standard deviation of 15. **Table 6** outlines the secondary outcome measures, which encompassing evaluations of the effectiveness of each intervention component.

Table 6. Primary and secondary outcome measures

Outcomes	Instrument or method
Primary outcomes	Total scale index score of RBANS (range, 40–160)
Secondary outcomes	
Cognition	Mini-Mental State Examination (range, 0–30)[13]
	Clinical Dementia Rating scale-Sum of Boxes (range, 0–18)[26]
	Prospective Retrospective Memory Questionnaire (range, 16–80, participant & informant)[27]
Mood	Geriatric Depression Scale-15 items (range, 0–15, participant)[28]
Disability	Bayer Activities of Daily Living (range, 1–10, informant)[29]
Quality of life	Quality of life-Alzheimer's disease (range, 0–52, participant & informant)[30]
Physical function	Global Physical Activity Questionnaire (participant)[31]
	Short Physical Performance Battery (range, 0–12)[32]
	Sit-to-stand for 30 sec
	Walk in place for 2 min
Nutrition	Nutrition Quotient for Elderly (range, 0–100, participant)[33]
	Mini-Nutritional Assessment (range, 0–14)[34]
Vascular risk factors	Blood pressure, body mass index, waist circumference, smoking, alcohol consumption, lipid profile, hemoglobin A1c, glucose
Motivation	Self Determination Index (range, −66–66, participant)[6]
Sleep	Pittsburgh Sleep Quality Index (range, 0–21, participant)[35]
Progression	Conversion to dementia
Tolerability	Retention rate
Adherence	
Adverse event	
Exploratory outcomes	Brain-derived neurotropic factor
	Neurofilament light chain
	Glial fibrillary acidic protein
	Ptau181
	Polygenic risk score in Alzheimer's disease
	Korean Version of Cognitive Reserve Index Questionnaire[36]

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

Whether the sessions are conducted at a facility or through the ZOOM platform or telephone, adherence to both group and individual interventions will be evaluated based on real-time attendance at the intervention sessions. The tablet-based cognitive application will be configured to allow administrators to view all participants' data on the administration homepage. Study coordinators will be able to evaluate adherence to the self-administered cognitive training sessions at home through the administration homepage. Tolerance will be assessed based on the retention rate. The retention rate will be used to calculate the percentage of participants in each group who have not dropped out at the end of the study.

Exploratory outcomes

Exploratory studies are planned to investigate how the multidomain intervention program works in the brain (**Table 6**). Changes in plasma ptau181, serum brain-derived neurotrophic factor (BDNF) as a biomarker of neuroplasticity, plasma neurofilament light chain as a biomarker of neurodegeneration, and plasma glial fibrillary acidic protein as a neuroinflammatory marker will be investigated following the multidomain intervention. All four assessments will be conducted using the Single Molecular Array (Simoa) technique (Quanterix Corp., Boston, MA, USA). Cognitive reserves will be assessed using the Cognitive Reserve Index Questionnaire,[36] and AD polygenic risk scores will be evaluated.

Study procedure

Prior to the commencement of the study, a workshop will be conducted to educate all assessors and individuals who will be implementing the intervention on the proper procedures for performing outcome measures or implementing the programs. The RBANS will administered by the same psychologist during the baseline assessment, at week 12, and within four weeks after the intervention. The other secondary and exploratory outcomes will be evaluated four weeks before the intervention and within four weeks after the intervention. Study coordinators will assess real-time intervention program adherence and monitor adverse events (AEs). The safety committee will meet regularly to assess any AEs that emerge. Participants who withdraw prematurely will be instructed to complete all endpoint assessments at early termination. Participants taking antidepressants, anxiolytics, or acetylcholinesterase inhibitors, who have consumed stable doses for more than eight weeks before the baseline, will continue taking such medications without dose changes until the end of the study.

Criteria for early discontinuation

The conditions for early discontinuation will include 1) withdrawal of participant consent, 2) unavoidable circumstances such as moving to a different residence or loss to follow-up, and 3) an investigator's decision to terminate for the participant's welfare or health. Non-adherence will not lead to termination, nor will the development of dementia during the study.

Data management

Study coordinators will complete data entry at each center. The data quality will be improved through automatic range examination of the data values. The data collected in this study will be monitored by an independent monitor in accordance with Good Clinical Practice (GCP) guidelines and clinical research protocols. Only authorized users will have access to the data system.

Sample size estimation

In our previous study, the difference in RBANS total scale index score between the control and HMI groups was found to be 6.2.[6] The standard deviation of the RBANS total scale index score was 19.8 in the control group. The autocorrelation of the RBANS total scale index

scores between the baseline and study end was 0.8 in the control group. In the present trial, three evaluations of the RBANS will be conducted. To achieve a power of 0.8 for detecting a significant difference (p=0.05, two-sided) using the time-averaged difference of repeated measures in the power analysis and sample size program, PASS 11 (NCSS, Kaysville, UT, USA), it is necessary to have 134 participants in each study group. Anticipating a dropout rate of 10.5%, based on our previous report,[6] the necessary sample size is estimated to be 300, with 150 participants per group.

Statistical analysis

The endpoints will be evaluated within a modified intention-to-treat population, encompassing all randomized participants who have undergone a baseline assessment and at least one post-baseline evaluation and who—if assigned to the intervention group—have engaged in the intervention program at least once. Additional analyses on per-protocol populations will also be performed. We will use a chi-square test for categorical variables and a Student's *t*-test for continuous variables to compare the baseline characteristics between the groups. Changes in the RBANS total scale index score will be compared between the intervention and control groups using a linear mixed model with group, visit, group × visit interaction, and baseline scores as fixed effects. Analysis of covariance with a baseline score as a covariate will be used to compare changes from baseline to the study endpoint in the secondary outcomes as well as exploratory blood biomarkers between the intervention and the control groups.

The safety analysis will be performed on all participants who undergo at least one safety evaluation post-baseline and who—if assigned to the intervention group—participate in the intervention program at least once. The chi-square test will compare the incidence of AEs, adherence, and retention rates between the intervention and control groups.

Ethics and dissemination

This study will be conducted in accordance with the International Conference on Harmonization GCP Guideline. This study has been approved by the Inha University Hospital Institutional Review Board (IRB, INHAUH-2021-06-040), the Ewha Womans University Seoul Hospital IRB (SEUMC-2021-07-037), the Ewha Womans University Mokdong Hospital IRB (EUMC-2021-08-003), the Ajou University Hospital IRB (AJIRB-BMR-SUR-21-323), the Bobath Memorial Hospital IRB (P01-202109-11-002), the Dong-A University Hospital IRB (DAUHIRB-21-168), the Chonnam National University Hospital IRB (CNUH-2021-326), the Hanyang University Hospital IRB (HYUH-2021-07-041), the Myongji Hospital IRB (MJH-2021-08-032), the Jeonbuk National University Hospital IRB (CUH-2021-08-043), the Pusan National University Hospital IRB (2108-016-015), the Konkuk University Hospital IRB (KUMC-2021-08-023), the Samsung Medical Center IRB (SMC-2021-08-022), the CHA Bundang Medical Center IRB (CHAMC-2022-01-020), the Catholic Kwandong University International St. Mary's Hospital IRB (IS22EIMI0008), the Daejeon Eulji Medical Center IRB (EMC-2021-12-004), and the Uijeongbu St. Mary's Hospital IRB (UIRB-2022-0428). Protocol modifications will be reported and approved by each center's IRB. All potential participants will provide written informed consent and additional consent for collecting and using biological specimens facilitated by a study doctor before participating in the study. All participants' names and privacy will be kept confidential, and they will be identified by the numbers assigned during the study. The results will be presented at national and international conferences and published in peer-reviewed journals. Researchers will be eligible for authorship after consideration by the principal investigators. No professional writers will be used. Access to the raw data will be available from the corresponding authors on reasonable request.

Public and patient involvement

Other members of the public or patients do not play any role in designing, conducting, reporting, or spreading the findings of our research.

DISCUSSION

As of 2017, South Korea has transitioned into an aged society, with over 14% of the population ≥65. It is anticipated to evolve into a post-aged society before long, with >20% of the population projected to surpass 65 by 2025.[37] A nationwide survey showed that the prevalence of MCI in South Korea is approximately 24%–27%.[37,38] As the population continues aging, the prevalence of MCI is expected to increase further. There is therefore a very urgent need to prevent progression to dementia at the MCI stage. Recently, lecanemab and donanemab have been developed for the treatment of early AD, including MCI.[39,40] However, these drugs do not entirely halt the progression of AD, they are associated with side effects like infusion-related reactions and amyloid-related imaging abnormalities, and they are costly. Moreover, there is currently no treatment for MCI resulting from causes other than AD. Further, in MCI caused by AD, a multidomain intervention may offer the potential for a synergistic or additive impact with the new drugs. Initially, we sought to develop an effective multidomain intervention program without incorporating a new drug by demonstrating its effectiveness and safety in MCI.

In the previous study, the HMI group demonstrated remarkable outcomes comparable to those seen in the FMI group, where all interventions occurred at a facility.[6] In terms of the RBANS total scale index scores, the enhancement within the HMI group closely resembled that within the FMI group. The HMI participants demonstrated slightly higher retention and adherence rates than those in the FMI group. Over time, the HMI program could prove to be a more economical choice because of its decreased labor costs and lack of venue-related expenses. The previous report also proposed the HMI program as a particularly viable alternative during times when opportunities for outdoor activities are restricted, such as during the global COVID-19 quarantine phase or during periods of severe air pollution. As this study was initiated during the COVID-19 pandemic, we decided to follow the HMI schedule. Moreover, as a fully non-face-to-face intervention is likely to result in decreased compliance among older people, it was decided to implement the HMI schedule in a hybrid model that integrated both in-person and remote programs.

In the previous study, participants in the HMI group performed exercises at home while watching videos on a tablet PC or while following instructions on a booklet or poster.[5,6] They did not perform exercises using the ZOOM platform. Therefore, the study coordinators assessed adherence to the home exercise sessions by comparing participants' written self-reports of the day and time of exercise with the corresponding data recorded by a Fitbit smartwatch (Fitbit, Inc., San Francisco, CA, USA) that they wore on their wrists during daily activities. The study coordinators cross-referenced the written self-reports with the activity recorded by Fitbit. However, it is of course still possible that adherence to the exercises performed at home was not accurate and that the participants did not perform the exercises as vigorously as they would have at a facility. While the FMI group showed a significant increase in serum BDNF levels compared to the control group, the absence of such a difference from the control group in the HMI group suggests that the participants in the HMI group might not have exercised at home as hard as the corresponding participants did at the

facility.[6] To address this issue, in the current study, we will utilize the ZOOM platform for real-time home exercise sessions conducted by a qualified exercise professional.

The crucial importance of social distancing amid the coronavirus pandemic led to a swift evolution in digital communication. In particular, there was a surge of work-related meetings and conferences using non-face-to-face platforms like ZOOM.[11] However, older people who do not work and who therefore did not personally experience this change may be less familiar with digital communication platforms. In particular, older Korean adults commonly use KakaoTalk and YouTube on their smartphones, but they may still be unfamiliar with other applications and tablet PCs. The ongoing progress in digital technology holds significant promise for fostering healthy aging in older adults. Previous studies have reported that digital technologies can have substantial impacts in preserving functional independence, preventing injuries, fostering social connections, and playing a role in addressing mental health conditions in older adults.[41] Studies are actively examining the use of digital platforms for multidomain interventions in high-risk groups for dementia among older adults.[42,43] However, there have to this point been few multidomain intervention studies that have used a digital application and video communication platform while targeting only MCI. This study is therefore expected to help determine whether intensive multidomain interventions using digital technologies are effective in MCI.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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