Table 5 Factors associated with caregiver burden regarding instrumental/basic activities of daily living, age and sex

	NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
IADL men												
Ability to use telephone	−0.322	0.026	−0.390	0.009	−0.499	0.001					−0.390	0.009
Mode of transportation					−0.290	0.033	−0.300	0.001	−0.263	0.032		
Ability to handle finances							−0.329	<0.001				
Responsibility for own medication									−0.287	0.020		
Age			−0.324	0.028							−0.324	0.028
IADL women												
Mode of transportation	−0.305	0.013					−0.187	0.001	−0.173	0.019		
Shopping			−0.386	0.001	−0.258	0.033						
Food preparation					−0.305	0.012	−0.220	<0.001				
Responsibility for own medication							−0.219	<0.001				
Ability to handle finances							−0.125	0.022	−0.245	0.001	−0.400	<0.001
BADL												
Fecal incontinence	−0.219	0.018										
Transfers (bed to chair and back)	−0.202	0.029										
Climbing stairs			−0.219	0.014								
Bathing					−0.769	<0.001						
Grooming					0.535	0.002						
Urinary incontinence							−0.251	<0.001				
Dressing							−0.196	<0.001	−0.297	<0.001	−0.276	0.011
Age			−0.204	0.023			0.136	0.003				
Gender (male)			0.204	0.023	0.213	0.013						

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Instrumental activities of daily living (IADL) were evaluated using the Lawton Index (LI), and basic activities of daily living using the Barthel Index (BI). Dependent variables were summed scores of Zarit Burden Interview, and dependent variables were subitems of LI or BI, which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

Table 6 Factors associated with caregiver burden regarding presence or absence of comorbid conditions of geriatric syndrome

Geriatric syndrome	NC		aMCI		AD29–24		AD23–18		AD17–12		AD11–0	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Falls					0.190	0.035			0.162	0.008		
Cough/sputum					0.185	0.038						
Diarrhea/constipation					0.209	0.020						
Palsy							0.209	<0.001				
Sleep disturbance							0.119	0.012			0.230	0.035
Urinary disturbance									0.182	0.003		
Fatigue									0.162	0.010		
Ringing in the ear											0.217	0.047
Age							0.178	<0.001				
Sex (male)					0.243	0.007	0.133	0.004				

The patients were divided into six groups: normal cognition (NC), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD) 29–24, AD23–18, AD17–12 and AD11–0 (AD patients were subclassified into four groups by Mini-Mental State Examination score). Dependent variables were summed scores of Zarit Burden Interview, and dependent variables were comorbid general symptoms (presence or absence), which were entered in a stepwise fashion into multiple linear regression analyses. Standardized β-values and *P*-values are shown.

with CB. At the same time, Verbal aggressiveness, such as unwarranted accusations and swearing, and Apathy were other prominent factors associated with CB. Individuals with aMCI might tend to be easily upset, with a lack of control over their impulses when their errors are pointed out, as they might feel distressed by difficulty coping with things they had previously been able to do easily, because of cognitive decline. In contrast, awareness of cognitive decline might exert influences on negative symptoms including apathy, as patients tend to lose motivation as it gradually becomes difficult for them to maintain social interaction, enjoy hobbies and even deal with daily activities.

Although total LI score was not changed in our patients with aMCI (Table 2), recent research has shown that individuals with aMCI have slight functional impairment.[21] Among IADL, functions related to social roles and engagements deteriorated first, followed by those related to domestic roles, and finally those related to personal tasks.[22] Deficits in telephone use in men and shopping in women could be candidate factors for CB. It seems likely that the inability to use a telephone disturbs the family caregivers' social life through miscommunication, and impairment of shopping has to be supported by other family members.[23]

In cognitive stage of AD29–24, positive and passive symptoms of BPSD and impaired IADL were prominent in CB. Motor aggressiveness including destructive behavior was a burden factor. In AD, aggressiveness is one of the most frequent BPSD, with a prevalence of over 70% in AD,[24] and aggressiveness can be a single determinant of caregiver burden and early institutionalization.[25–28] Behavior disturbance, such as Waking up at night and Pacing up and down, were also factors associated with CB. Mobility of an AD patient might increase CB, as such patients require extra attention and supervision, which might in turn cause a more stressful situation for caregivers.[29] Apathy, a syndrome of decreased initiation and motivation, is one of the most common BPSD, with a prevalence of over 70% in AD.[30] In the course of AD progression, apathy becomes more severe as degeneration of frontosubcortical circuits develops.[31] It is also problematic that apathy is associated with deterioration of ADL because of the patient's indolence and inactivation of goal-directed cognitive activity, which increases the workload and stress of their caregivers.[32]

Regarding IADL, in addition to factors related to social roles (telephone use and transportation in men) and those related to domestic roles (shopping and food preparation in women), those related to personal tasks were associated with CB in this stage. Deficit in using transport might trigger withdrawal and accelerate passiveness. Regarding BADL, impaired grooming and bathing could contribute to CB.

In stage of AD23–18, BPSD, IADL and geriatric syndrome were associated with CB. Verbal aggressiveness and Behavior disturbance, as well as Apathy, were important factors. Daytime sleepiness and comorbidity of sleep disturbance were associated with CB, both of which could have a severe negative impact on the physical and mental health of both patients and caregivers. Day–night reversal and sleep disturbance might trigger BPSD, such as agitation, irritability and apathy, resulting in the breakdown of community-based care. Furthermore, incontinence (mostly urinary incontinence) was also associated with CB, although the prevalence of urinary incontinence in this stage was 15.0%.

Caregivers of patients with urinary incontinence have higher levels of stress and depression than those caring for people with other conditions, and incontinence leads to early institutionalization.[33–35]

Regarding IADL, deficits in handling domestic finances and transportation were common factors associated with CB in men and women. It is time-consuming and often stressful for caregivers to take over the financial responsibilities of the household.[29,36] Non-compliance with medication in women would cause caregivers mental stress. Regarding BADL, dressing was a candidate factor for CB in AD patients with more severe cognitive dysfunction. AD patients might often refuse to be helped with personal care including changing their clothes, which causes stress to their caregivers.

In cognitive stage of AD17–12, BPSD, IADL and geriatric syndrome were also associated with CB. BPSD were worse and care burden became more severe. Regarding IADL, caregivers were annoyed with the patients' deficits in their own personal tasks, such as in the use of transportation (in men and women) and in self-medication (men). Deficit in handling finances was still shown to be an associated factor in women. This could have been related to a lack of awareness by patients of a deficit.[36] Patients who are unaware of functional deficits often overestimate their ability and believe they are capable of activities beyond their capabilities, which can cause problems and stress in caregivers. As comorbidity, falls indicate further deterioration of motor function, and fatigue might reflect and accelerate passiveness.

In AD11–0, prominent factors for CB were BPSD, including Motor aggressiveness and Behavior disturbance. The frequency of BPSD related to CB markedly increased at this stage. For instance, agitation is a symptom related to frontal lobe dysfunction, with a prevalence of nearly 50% in AD.[37,38] It can be triggered by physical problems, such as pain and lack of sleep; psychiatric problems, such as anger, aggressiveness, anxiety and depression; environmental stresses, such as noisiness and inadequate temperature; and as a side-effect of medication. Agitation can also be a single determinant of early institutionalization.[25–28]

Although sleep disturbance and ringing in the ears could be associated with CB in this stage, the contribution of geriatric syndrome to CB was not obvious (Table 3). In this connection, it should be noted that participants in the present study were outpatients without serious physical complications. Alternatively, the increment of BPSD might have obscured the role of geriatric syndrome as a burden factor in the analysis with a relatively small number of participants ($n = 87$).

This study clearly indicated that various differential factors were cognitive stage-dependently associated with CB. It should be stressed that the higher prevalence of BPSD, geriatric syndrome and impairment of life function in particular cognitive stages was not always a burden factor. For instance, symptoms of Behavior disturbance in AD29–24 were not as frequent as in AD11–0, but were factors responsible for CB. Urinary incontinence was markedly increased in cognitive stages of AD11–0, but was associated with CB even in AD23–18. It seems likely that caregivers are surprised and embarrassed by their first experience of problematic symptoms of dementia in patients who have moderate cognitive dysfunction. It is therefore important to know and predict these burden factors in advance. Second, even if certain factors showed an association with CB in one cognitive stage, they did not always remain burden factors in subsequent cognitive stages. Different activities of IADL were shown to be burden factors in particular cognitive stages.

The results of the present study suggested that prevention of BPSD and comorbidity of geriatric syndrome is an essential consideration in the management of AD. At the same time, life care support for deteriorated IADL should be considered even for patients belonging to AD29–24. Treatment of BPSD and comorbidity could be beneficial in ameliorating CB, as comorbidity can cause various BPSD, and BPSD increase the risk of geriatric syndrome, such as falls and muscle weakness, and vice versa. It was reported that half of BPSD were caused by comorbidity and medication; in AD, 23% of BPSD are caused by medication, 18.3% by comorbidity and 6.7% by a combination of the two.[39] It is well established that physical rehabilitation is effective for not only the prevention of falls/motor disturbance, but also improvement of mood, apathy and day–night reversal.

Previous studies have shown that individualized educational and support programs for caregivers are effective to ameliorate CB.[40,41] Educational programs should provide prognostic information on the disease of dementia, as well as factors associated with CB. In this respect, the findings of the present study might be informative for caregiver education.

The present study had several limitations. It was a cross-sectional study. A second limitation was selection bias of the study participants, although the participants were composed of a large number of patients consecutively selected in the Medical Center for Dementia at the NCGG. All data were obtained from outpatients, and inpatients suffering from various physical complications, such as recurrent pneumonia and fractures, were not included. Finally, CB is comprised of multidimensional factors including patient factors, such as the severity of disease, premorbid characteristics, and financial and social status, caregiver factors, and other environmental factors, all of which are highly individualized.[42] The present study mainly analyzed burden factors on the patients' side. To clarify the multifactorial mechanisms of CB, more detailed information on

demographics, socioeconomic conditions and use of several care services need to be analyzed. However, our observation provides important information on CB, which might reflect general attitudes of caregivers to demented older adults, when they first attended a medical center for consultation on dementia. Longitudinal follow-up studies of demented older adults with detailed information on CB are required.

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Disclosure statement

The authors declare no conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Prevalence of Dementia Behavior Disturbance Scale (DBD) subitems in subjects with normal cognition (NC), amnestic Mild cognitive impairment (aMCI) and Alzheimer's disease (AD)29–24, AD23–18, AD17–12, and AD11–0.
Figure S2 Prevalence of symptoms of geriatric syndrome in participants with normal cognition (NC), amnestic mild cognitive impairment (aMCI) and varying stages of Alzheimer's disease (AD).

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Community-Based Intervention for Prevention of Dementia in Japan

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Abstract

Population aging is accelerating, with prolonged life expectancy and a decrease in birth rate. As age is a significant risk factor for dementia, we are confronted with an ever-increasing prevalence of mild cognitive impairment (MCI)/dementia. Thus, the Japanese National Center for Geriatrics and Gerontology launched a project to promote community-based research, including the development of an effective screening system for high-risk groups and intervention for dementia prevention. This review introduces the project, the Obu Study of Health Promotion for the Elderly, with the following strategic triad: 1) Identification of the target population by population screening; we regarded patients with MCI as the target population, and developed a screening test battery to identify MCI in a population screening setting. 2) Scientific evaluation of community-based intervention; we developed an interventional method combining exercise and cognitive training ("cognicise"). In practical settings, "cognicise" is programmed into multicomponent exercise intervention, which was reported to have benefits of cognitive improvement and reduction of brain atrophy based on randomized controlled trials. 3) Standardization of the methods of population screening and community-based intervention for evidence-based policy making and widespread implementation. Dementia prevention, or at least delaying the onset of dementia and/or stopping/slowing the progression of dementia, should benefit the whole society as well as individuals. It is our continuing challenge to improve the screening system and community-based intervention for dementia prevention through accumulation of evidence .

Key words: Identification of the target population, population screening system, multicomponent exercise intervention, cognicise, evidence-based policy making.

This review introduces the research project of community-based dementia prevention by the National Center for Geriatrics and Gerontology (NCGG), the Obu Study of Health Promotion for the Elderly (OSHPE). As a forward-thinking strategy in Japan, the National Center leads research on dementia prevention, and returns the results of research to society for promotion of nationwide preventive intervention.

Social background: Aging "tsunami" and long-term care insurance system in Japan

The population is aging at an accelerated rate, with increasing life expectancy and decreasing birth rate; the total population is declining while the older population ratio keeps increasing with prolonged life expectancy, especially that of the old-old aged 75-84 and the oldest-old aged over 85. As the risk of developing MCI and dementia increases with age, the prevalence of MCI and dementia increases in parallel with the enlargement and deepening of the aging society. In 2010, the prevalence of dementia and MCI was estimated to be 15% (4.39 million, 95% confidence interval (CI): 12-17%) and 13% (3.80 million, 95% CI: 10-16%), respectively (1), and since then, the prevalence rate is ever-increasing. We should face up to the reality that the social burden on the productive-age population exerts a considerable impact on the national economy. Accordingly, the fight against dementia is now the most challenging issue in Japan, and strategies for dementia prevention should be regarded as one of the national priorities of healthcare policies in terms of the national economy as well as individuals' health.

Long-Term Care Insurance Act

With the intention of sharing the social burden of the aging society, the Japanese public Long-Term Care Insurance Act was launched in April 2000 as a sustainable social security system. People over 40 years of age pay a premium for care insurance, and those who are qualified under this system receive care services.

Provision of preventive services was commenced to help elderly persons maintain or regain independence, under the revised Act of 2006, with greater emphasis on a "Preventive Long-Term Care". The revision was based on the "Emergency Project for Improvement of Medical Care and Quality of Life for People with Dementia", which focused on prevention, as well as improvement of diagnostic techniques, development of treatment regimens, and provision of adequate long-term care. According to the Act, local municipalities established "Comprehensive Community Support Centers" (CCSCs), which are expected to build a platform and network for preventive activities (2). In agreement with the concept of community-based rehabilitation, municipality-led preventive interventions conducted by CCSCs have been encouraged under the leadership of the Ministry of Health, Labour and Welfare of Japan (3). In response, many municipalities initiated preventive intervention as a service for community dwellers. However, the problem

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is that the municipalities have undertaken interventions without reliable evidence of prevention of cognitive decline and dementia.

Community-based preventive intervention promoted by the National Center for Geriatrics and Gerontology

For effective intervention and efficient use of social security expenses, preventive interventions should be conducted based on scientific evidence. Thus, NCGG has launched research projects to verify the practical efficacy of the community-based programs including the population screening system and dementia preventive measures since 2010: Obu Study of Health Promotion for the Elderly (OSHPE) project.

Obu Study of Health Promotion for the Elderly: OSHPE

The OSHPE strategic triad is:

1) Identification of the target population by population screening

2) Scientific evaluation of community-based intervention

3) Standardization of method of population screening and community-based intervention for evidence-based policy making and widespread implementation

Population-based approach for identification of high-risk individuals

For effective preventive intervention, ongoing research and intervention focus on the elderly with MCI as high-risk individuals for dementia.

Target population: MCI

The concept of MCI has been proposed to identify individuals at a transitional stage between normal aging and clinically probable Alzheimer disease (AD). A longitudinal epidemiological study conducted in Japan reported that the conversion rate of MCI to AD was 3.7% in 3 years, whereas 0.2% of those without MCI developed AD (4). MCI, which shows heterogeneous pathological features, is classified broadly into amnestic and non-amnestic types; amnestic MCI primarily affects memory and shows a higher rate of progression to AD (5-7).

We defined MCI based on previous studies (6, 8-11), using the following criteria: subjective memory complaints, cognitive impairment (indicated by an age-adjusted score at least 1.5 standard deviations (SDs) below the reference threshold of any of the tests, all of which are commonly used for detailed neuropsychological assessments); no evidence of functional dependency (no need for supervision or external help in performing activities in daily life); and exclusion of the clinical criteria for dementia.

In the clinical setting, MCI and dementia are ideally diagnosed by careful history taking and medical interview. In the setting of population screening where diagnosis is made at the first contact within a limited time, the challenge is to improve the sensitivity and specificity of screening. At present, there are no screening measures whose sensitivity and specificity are high enough to avoid false-positive and false-negative results (12). In cases of false-positive diagnoses, people would suffer from incidental findings, and patients with false-negative results would miss the chance to receive optimal care at the reversible stage of disease. Under such circumstances, our efforts are focused on maximizing the accuracy of population screening. At the same time, we are proceeding with the project cautiously in consideration of the feelings and thoughts of each participant, as undergoing the screening process itself can pose a psychological burden on participants.

National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT)

To identify MCI, we developed a multidimensional neurocognitive functional assessment tool using a tablet personal computer (PC); the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT), which consists of eight tasks used to assess logical memory (immediate and delayed recognition), word list memory (immediate and delayed recall), attention and executive function (tablet version of Trail Making Test-part A and B), processing speed (tablet version of Digit Symbol Substitution Test), and visuospatial skill (figure selection). The participants were given 20 to 30 minutes to complete the battery, which consisted of these eight tasks. High test-retest reliability and moderate to high validity have been confirmed in community-dwelling older adults for all task components of the NCGG-FAT.[13] NCGG-FAT is easily administered using a tablet PC, which reduces tester bias and enhances accuracy of data processing and analysis. Screening for MCI included a standardized personal interview for collection of sociodemographic, lifestyle, medical history, and functional status (activities of daily living) data, along with cognitive screening conducted using the Mini-Mental State Examination (MMSE) (14) and the NCGG-FAT (13).

Scientific evaluation of community-based intervention

Since strategic efforts are required for prevention of MCI and frailty, especially provision for the old-old

and the oldest aged over 75, our intervention aimed to achieve co-benefits of cognitive improvement and enhancement of physical function by exercise intervention. Previous studies reported supportive evidence for a relationship between cognitive and physical function (15, 16) and our data also suggested a correlation between improvement of general cognitive function and that of physical performance brought by exercise intervention in those with MCI (17, 18).

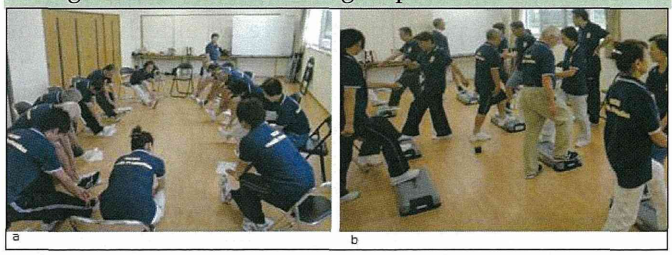
This section focused on the scientific evaluation of benefits for dementia prevention, as it would be almost self-evident that exercise is beneficial for prevention of physical frailty. The identification of high-risk persons for dementia would ideally provide chances for them and their families to receive optimal treatment at an earlier stage, which could delay the onset of dementia and/or stop the progression of dementia, or at least lead to an improved prognosis. However, it is still unclear whether non-pharmacological intervention is clinically beneficial for patients or not (12). Under the present situation, we are continuing efforts to develop intervention measures that could delay the onset of dementia and/or stop/slow the progression of dementia, and establish scientific evidence with randomized controlled trials (RCT). Ultimately, we set two perspectives for the dementia prevention project goals: at the individual level, improvement of each person's quality of life (QOL) as well as cognitive function, and at the community level, community revitalization and reduction of social security cost (13, 19, 20).

Multicomponent exercise intervention

With the expectation of synergistic effects of exercise and cognitive stimulation, we have developed an intervention method, "cognicise", which is a multicomponent exercise program with cognitive loads, e.g., learning tasks during the exercises. Previous studies reported that regular exercise is beneficial in reducing the risk of cognitive decline in elderly individuals (21-24). Regarding cognitive stimulation, substantial evidence has suggested that the risk of cognitive decline is lower in those who are more mentally active than in inactive individuals, and it is well established that dual tasks place a load on the prefrontal cortex (23). Thus, "cognicise" may generate synergistic effects for risk reduction of cognitive decline (25).

In the practical setting of intervention, "cognicise" is programmed into multicomponent exercise (Figure 1). A typical setting is as follows. The intervention is conducted in a group of around 15-25 participants with two trained physiotherapists. The session begins with a 10-minute warm-up and stretching exercise, followed by 20 minutes of muscle strength exercise. Then the participants undergo 60-minute circuit training consisting of stair stepping, endurance walking, and walking on balance boards, which includes the components of aerobic exercise and postural balance retraining. The mean intensity of the aerobic exercise was approximately 60% of maximum heart rate, which was similar to the intensity used in previous studies (22, 26). The circuit training is conducted partly as "cognicise" in the dual-task mode where the participants were requested to perform cognitive tasks during exercise, e.g., to invent a poem while walking, or to memorize step patterns in a consecutive manner while stepping as quickly and accurately as possible in ladder training. It should be noted that exercise in dual task mode might cause more adverse events such as falls or fractures than ordinary exercise.

Figure 1AB. Scenes of multicomponent exercise intervention. The uniform enhances the participants' feeling of involvement in the group.



Another significant merit of exercise intervention is that there found no evidence of increased serious adverse effects due to interventions in the participants. (12). Cognitive training inevitably identifies what those with cognitive decline including MCI are incapable of. Awareness of deficits can devastate their self-confidence and lead to reduction of QOL (27). Until the mid-1980s, cognitive training such as reality orientation training was often conducted in a confrontational atmosphere, and adverse effects such as frustration, anxiety, depression, and lowering of self-esteem were reported (28, 30). In response, the consensus statement of the American Association for Geriatric Psychiatry (AAGP) Position Statement warned of potentially harmful effects of cognitive training conducted in a confrontational atmosphere (31).

Self-monitoring and social interaction

The program contains the component of behavioral intervention. Following baseline monitoring, participants were asked to monitor and record the daily step count and daily duration of moderate physical activity using the pedometer/accelerometer. During the study period, participants were instructed to wear a triaxial pedometer/accelerometer on their hip. Daily home-based exercise in addition to a structured program was encouraged. The participants were requested to record step count and moderate activity on a physical activity chart, and at each session, the participants received motivational feedback. As a group activity, the participants supported each other's efforts to maintain

a continuous self-improvement process. Although the causal link is controversial, epidemiological studies suggested that greater participation in social activities correlated with lower risk of cognitive decline (31-35). As above, larger effects may be expected when exercise is conducted in combination with cognitive stimulation, behavioral intervention and social interaction.

Effects of intervention

Effects on cognition

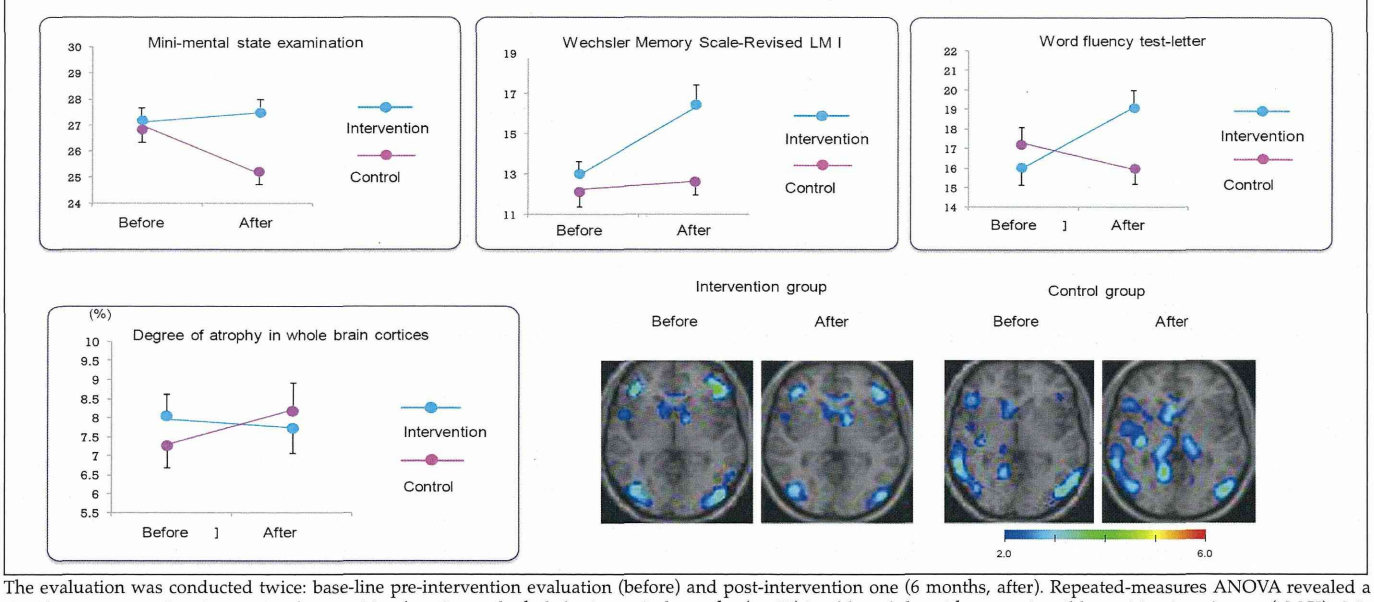
In the OSHPE project, interventional research was continuously implemented, and in the following section, two cases are presented. The first case is a 12-month intervention conducted with a RCT design(36). The participants were 50 elderly persons (27 men) with amnestic MCI aged between 65 and 93 years (mean age, 75 years), who were randomized to either a multicomponent exercise intervention group (n = 25) or a control group (n = 25). The intervention was conducted under the supervision of physiotherapists for 90 minutes/day, 2 days/week, a total of 80 times over 12 months. Subjects in the control group attended three health education classes during the 12-month period. Interim (after 6 months) and post-intervention assessments of cognitive function were conducted. Repeated-measures ANOVA revealed significant interaction effects (group × time interactions) in MMSE ($p = 0.04$), logical memory of immediate recall ($p = 0.03$), and letter verbal fluency test ($p = 0.02$) (36).

This intervention was evaluated highly as a reliably designed study in the systematic review by the U.S. Preventive Services Task Force concerning dementia prevention for those with MCI. Among exercise interventions, two studies were evaluated as showing reliable intervention with a benefit in global cognitive function (approximately 1 point on MMSE or ADAScog) at 12 to 18 months: the OSHPE study and the trials conducted by Lautenschlager et al. in 2008 (12, 22). More high-quality well-designed interventional research is still needed, since the systematic review concluded that there was insufficient evidence to determine whether there is a clinically important benefit of exercise intervention or not.

Reduction of brain atrophy

The following study analyzed atrophy of the brain as a manifestation of physiological change (37). The participants were 100 elderly persons (mean age, 75 years) with MCI, who were subclassified into an amnestic MCI group (n=50) and non-amnestic MCI group (n=50) before randomization. The intervention was conducted for 90 minutes/day, 2 days/week, 40 times in 6 months. Repeated-measures ANOVA revealed no group × time interaction in the total MCI patients, whereas sub-analysis of amnestic MCI patients for group

Figure 2. Changes in cognitive function and whole brain volume in response to 6-month intervention



The evaluation was conducted twice: base-line pre-intervention evaluation (before) and post-intervention one (6 months, after). Repeated-measures ANOVA revealed a significant group x time interaction for cognitive function and whole brain cortical atrophy ($p<.05$) in older adults with amnestic mild cognitive impairment (aMCI) : Mini-mental state examination, Wechsler Memory Scale-Revised, Word fluency test (letter), and degree of atrophy in whole brain cortices. Group mean and standard errors are shown with the blue and pink lines indicating the intervention and control groups, respectively. In analysis of brain volume, we used a voxel-based specific regional analysis system for Alzheimer disease (VSRAD),[44] which enables examination of atrophy of the whole brain cortices using voxel-based morphometry. The gray matter image of each patient was compared with the mean and standard deviation (SD) of gray matter images of healthy volunteers using voxel-by-voxel Z score analysis; the Z score was calculated according to the following equation: (Z score = ((control mean)-(individual value))/control SD). The Z score reflected the degree of atrophy; if the Z-score was more than 2.0 within a voxel, the area was considered to exhibit atrophy. The left panels show whole brain cortical atrophy in a man (81 years old) with aMCI who completed the 6-month exercise program; whole brain cortices (WBC) atrophy decreased after the intervention (8.74% at baseline to 6.39% after the intervention). The right panels show WBC in a man (80 years old) with aMCI in the control group. The rate of WBC atrophy increased after the 6-month period (7.19% at baseline to 10.48% after the intervention).

× time interactions showed intervention effects in MMSE (p=.04) and logical memory of immediate recall (p=.04) and reduction of whole brain cortical atrophy (p<.05) in comparison with the control group (37) (Figure 2).

As the intervention is composed of multiple components, it is impossible to confirm a cause-effect relationship. Thus, accumulation of supportive evidence is indispensable, and we are continuing the study to elucidate the factors related to cortical atrophy. Regarding exercise, cross-sectional data suggested that aerobic exercise capacity and practice of moderate intensity exercise were related to hippocampus volume; aerobic exercise capacity was negatively correlated with atrophy of a specific brain area including the hippocampus in amnestic MCI, which is characterized by memory deficits (38). Among physical exercise, moderate intensity exercise was associated with hippocampus volume, whereas light intensity exercise was not (39). Besides, brain cortical atrophy is negatively correlated with trunk stability during dual task walking (40). Regarding higher function, brain cortical atrophy is negatively correlated with executive function tests such as Stroop Color and Word Test, (41) and household-related activities requiring planning in MCI subjects. (42) As these are the results of cross-sectional correlation analysis, multivariate analysis of longitudinal studies are required to analyze factors contributing to brain atrophy.

Standardization of method of population screening and community-based intervention for evidence-based policy making and widespread implementation

The mission of OSHPE is to promote standardization of screening and intervention programs based on evidence and to explore the feasibility of implementation of community-based approaches. As the national center, we are expected to return the results of research to society. NCGG should keep on improving the programs so that other municipalities can easily promote community-based approaches. Regarding feasibility, the multicomponent exercise intervention is simple enough to be implemented easily and effectively by other municipalities. Screening is also easily administered using the programs installed in tablet PCs. Cost effectiveness should be a major concern because dementia prevention strategies would have large public health implications in reducing economic and social burdens. The multicomponent exercise program could be conducted at a considerably low cost without any specific instruments.

Another concern is coping with the shortage of medical service personnel. The intervention of OSHPE was conducted under the supervision of physiotherapists to ensure accuracy as a research project. However, in practice, the multicomponent exercise program can be conducted by health care staff and/or volunteers who have undergone effective training programs. Training and organizing volunteers is included in our future plans to drive community-based preventive intervention. Those who have completed the training programs could become community facilitators to promote the prevention program widely throughout the community. Now, municipalities and CCSCs promote dementia prevention, but it is desirable that the preventive activities are initiated and organized by community dwellers autonomously.

Strategies of community-based prevention of OSHPE

Dementia prevention, or at least delay of the onset of dementia and/or stopping/slowing the progression of dementia, should benefit the whole society as well as each individual. Regarding the benefits for the participants, the target of our challenge is to improve quality of life (QOL) of each community-dwelling elderly person who may suffer from frailty and other geriatric syndromes as well as cognitive decline. Mere enhancement of cognitive function is not our aim. Optimal cognitive health is not just the absence of cognitive deficit, but rather an entity of cognitive and emotional health, which is tightly linked to physical health. "Health" should be evaluated holistically as a physio-psycho-socio-cognitive entity. One of the future challenges is to meet individual needs by population-based intervention, as one of the characteristics of the elderly group is its heterogeneity with a wide variety of individual needs. Community design is the purpose of OSHPE at the community level. Elderly individuals tend to feel alienated from society without social roles, and emotional isolation is associated with an increased risk of being alone with a housebound state and cognitive decline (32, 43). Participation in the intervention would help the elderly maintain ties with the community, and an increase in active senior citizens may lead to local revitalization and a reduction of social security costs.

We have just come to the starting point to establish evidence that exercise improves or supports, at least partly, cognitive performance in older persons with MCI. Although evidence suggests the possibility of delaying the onset of dementia and/or stopping/slowing the progression of dementia, longitudinal research is required to evaluate the prognosis including conversion from MCI to dementia and progression of the disease, for validation of preventive effects.

It is still an urgent issue to improve the screening system and community-based intervention for dementia prevention through accumulating evidence. Facing the most unprecedented ageing society, research on dementia prevention should be Japan's contribution to the world.

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