et al., 1999; Schinder and Poo, 2000). The neurotrophin hypothesis of depression is based on these functions of BDNF and postulates that depression results from stress-induced decreases in BDNF expression (Duman et al., 1997; Duman, Malberg, Nakagawa, & D'Sa, 2000). However, the majority of these studies have a small sample size or the design compares patients with major depression with healthy people. Extensive research is needed to determine the exact relationships between depressive symptoms and serum BDNF levels adjusted or controlled for potential confounders using large samples to examine the prevention strategies of depression in later life.

Another key factor that might affect the relationship between depression and cognition is age-related brain structural changes, especially hippocampal volume loss. Previous research has demonstrated reduced right hippocampal volume in older adults with depression (Bell-McGinty et al., 2002); moreover, depressed older adults with hippocampal volume loss were at greater risk of cognitive decline (Steffens et al., 2011). In addition, BDNF plays a role in regulating hippocampal plasticity: BDNF is presumed to be important for the integrity of the hippocampus and the maintenance of cognition. Normal aging appears to be associated with decreased BDNF signaling capacity in the brain. BDNF levels are decreased in hippocampal pyramidal neurons and dentate granule cells during aging in monkeys (Hayashi et al., 2001). These evidences suggest that a loss of BDNF plays a major role in the pathophysiology of depression, and that the neurotrophin hypothesis of depression appears to be valid especially when considered with relation to hippocampal function. However, it is not clear which cognitive categories are altered in patients with depressive symptoms and how BDNF levels might be associated to these and to hippocampal volume changes. The primary objective of this study was to examine which cognitive domains are associated with depressive symptoms and whether serum BDNF and brain atrophy are potential mediators between depression and cognitive decline in older adults.

2. Methods and materials

2.1. Participants

Our study assessed 5104 individuals who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE) (Shimada et al., 2013). Each individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. Each participant was 65 years or older at the time of examination (2011 or 2012), resided in Obu city, and had not participated in another study. We excluded participants who had been diagnosed with stroke ($n = 280$), Parkinson's disease ($n = 22$), or AD ($n = 8$); we also excluded those who had certified long-term care insurance needs ($n = 119$), functional decline in activities of daily living ($n = 11$), severe cognitive decline, i.e., mini-mental state examination (MMSE) 20 points or fewer ($n = 121$), or missing BDNF data or characteristics ($n = 191$). Ultimately, 752 of the 5104 participants were excluded and 4352 older adults (mean age 71.7 ± 5.3 years, range 65–97 years, 2085 men, 2267 women) were included in this study. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol.

2.2. Measurements: depressive symptoms and depression

The self-report screening instruments available to detect depression were deemed suitable for use in this community-based study. The 15-item version of the geriatric depression scale (GDS-15) has been validated as a screening tool for depressive symptoms in older people (Sheikh and Yesavage, 1986). A cut-off point of ≥5 on the GDS-15 has a pooled sensitivity of 88% and specificity 64%, and a cut-off point of ≥6 has a pooled sensitivity of 79% and specificity of 77% for diagnosing depression in older people (Dennis et al., 2012). A recent longitudinal study, which used GDS-15 and a cut-off score of 6, identified that MCI and subjective memory impairment were associated with incident depression (Weyerer et al., 2013). Participants were screened for depressive symptoms using the GDS-15 and a cut-off value of ≥6 to indicate clinically critical depressive symptoms. All participants completed a face-to-face interview including medical history by licensed and well-trained nurses. Depression was defined as follows: diagnosed as having depressive disorder by a family doctor and having received medication for depression.

2.3. Measurements: cognitive performance

Well-trained study assistants conducted assessments of cognitive functions. Prior to commencing the study, all staff received training from the authors in the correct protocols for administering the assessment measures. Cognitive tests were conducted using the MMSE (Folstein et al., 1975) and the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) (Makizako et al., 2013; Shimada et al., 2013). The computerized multidimensional neurocognitive task battery, the NCGG-FAT, comprises several cognitive domains: story memory (delayed recognition), word list memory (delayed recall), attention and executive function (tablet version of trail-making test, parts A and B), and processing speed (tablet version of symbol digit substitution task). In story memory, the participants heard a short story (approximately 1 min in length) through an auditory system using headphones. They were instructed to remember the details of a story, and then select the correct answer that described the details of the story from four choices after 20–30 min. All 10 questions in each task were shown and we calculated the total number of correct answers. Word list memory involved delayed recall of a 10-word target list. The participants were instructed to recall the 10 target words after approximately 20 min. The tablet version of trail-making test consists of part A and B, as well as the original written version of trail-making test. We recorded the time (in seconds) taken to complete each task, within a maximum period of 90 s in the tablet version of symbol digit substitution task, nine pairs of numbers and symbols were provided at the top of the display. A target symbol was shown at the center of the display. Participants then chose a number corresponding to a target symbol at the bottom of the display as rapidly as possible. The score was the number of correct numbers chosen within 90 s. One point was given for each correctly chosen number completed within the time limit. High test–retest reliability and moderate-to-high validity were confirmed in community-dwelling older adults for all task components of the NCGG-FAT (Makizako et al., 2013).

2.4. Measurements: potential correlates

With reference to the review articles by Cole and Dendukuri (2003) and Plassman et al. (2010), we selected four demographic variables, three physiological variables, two health status indicators, two blood biomarkers, and four behavioral variables as possible confounding factors of depressive symptoms and depression and cognitive decline (Table 1) (Cole and Dendukuri, 2003; Plassman et al., 2010). We selected four demographic variables—age, sex, educational level, and living alone—as possible correlates in determining the association between depressive syndromes and cognitive decline.

Table 1
Comparisons of potential confounders between the three groups.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics	
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	P
Age (years)	71.5	5.2	73.2	6.1	71.1	4.0	27.46	<0.001
Body mass index	23.4	3.1	23.2	3.1	23	2.9	2.65	0.071
Body fat (%)	28.2	7.9	28.5	7.5	29.6	7.7	1.48	0.227
Walking speed (m/s)	1.2	0.2	1.1	0.2	1.2	0.2	62.54	<0.001
Triglyceride (mg/dl)	152.9	93.1	155.3	103.5	155.5	85.7	0.19	0.831
HbA1c (%)	5.5	0.7	5.5	0.6	5.5	0.7	0.52	0.597
Frequency of going outdoors (times/week)	1.6	1.8	1.2	1.6	1.4	1.6	15.01	<0.001
Sleep time (min)	460.8	69.9	469.8	95.6	468.9	72.5	4.00	0.018
	%		%		%		Chi square	P
Sex (female)	52.0		50.9		63.2		4.66	0.097
Education (<10 years)	33.3		45.4		39.1		32.54	<0.001
Living alone (yes)	8.5		15.1		12.6		26.42	<0.001
Frailty (yes)	6.9		27.7		12.6		244.23	<0.001
Self-rated health (not well)	10.0		34.0		35.6		278.72	<0.001
Current smoking (yes)	10.0		8.8		13.8		2.35	0.309
Habitual exercise (no)	36.0		46.7		32.2		24.93	<0.001

The physiological variables were body mass index, percentage body fat, and walking speed. A multi-frequency bioelectrical impedance analyzer (MC-980A, Tanita Corp., Tokyo, Japan) was used to measure percentage body fat. This instrument uses six frequencies (1, 5, 50, 250, 500, and 1000 kHz) and the percentage body fat is calculated by multi-frequency bioelectrical impedance. Walking speed was measured on a flat and straight surface at a comfortable walking speed. Two markers were used to indicate the start and end of a 2.4-m walk path, with a 2-m section to be traversed before passing the start marker so that participants were walking at a comfortable pace by the time they reached the timed path. Participants were asked to continue walking for an additional 2 m past the end of the path to ensure a consistent walking pace while on the timed path.

Frailty and self-rated health were assessed as health status indicators. We considered the frailty phenotype to be characterized by limitations in three or more of the following five domains: mobility, strength, endurance, physical activity, and nutrition (Fried et al., 2001). We defined "good self-rated health" to be ratings of either "excellent" or "good" self-rated health, and we defined "poor self-rated health" to be ratings of either "not very good" or "poor" self-rated health.

Diabetes and hyperlipidemia are associated with cognitive decline, and we therefore measured HbA1c and triglyceride levels.

Behavioral factors, including current smoking, regular exercise, frequency of going outdoors, and sleep time were identified during the interview. Participants were asked whether they currently smoked or exercised regularly: responses were "yes" or "no". Participants were asked how often they traveled to places outside their town during a week and how long they slept during the day.

2.5. Measurements: potential mediators

Serum BDNF and brain volume were measured as potential mediators. All participants underwent BDNF measurement and 618 participants underwent brain volume assessments. Whole blood samples were collected from each participant by venipuncture. To obtain serum, the whole blood samples were allowed to coagulate at room temperature for 30 min and then centrifuged at room temperature for 15 min at 1000 × g. The collected serum was stored in polypropylene tubes at −80 °C until assayed. BDNF concentrations were quantitatively determined by enzyme-linked immunosorbent assay using the DuoSet ELISA Development Kit from R&D Systems (Minneapolis, MN). Assays were performed using a specific human BDNF antibody; no significant cross reactivity or interference was observed. Serum samples were diluted 1:50. Sample BDNF concentrations were then determined by nonlinear regression from the standard curves. Measurements were performed in duplicate and averaged to give a value in pg/ml, which was then expressed in ng/ml after correcting for sample dilution. "Low" and "high" concentration quality control pools were prepared by adding 10 or 100 ng to 5 ml portions of human serum (Innovative Research, Novi, MI), giving nominal concentrations of 2 and 20 ng/ml, respectively. The assays were performed by SRL Inc. (Tokyo, Japan).

Magnetic resonance imaging (MRI) was performed on a 3-T system (TIM Trio, Siemens, Germany) in a portion of the participants without diagnosis of depression ($n = 618$). Most participants who underwent an MRI had frailty ($n = 108$) or MCI ($n = 400$) who were not treated. Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (inversion time [TI], 800 ms; echo time (TE)/repetition time (TR), 1.98 ms/1800 ms; 1.1-mm slice thickness). Axial T2-weighted spin-echo images (TR, 4200 ms; TE, 89.0 ms; 5-mm slice thickness) and axial fluid-attenuated inversion recovery images (TR, 9000 ms; TE, 100 ms; TI, 2500 ms; 5-mm slice thickness) were obtained. We used voxel-based morphometry, an automatic whole-brain MRI analysis technique, to calculate the volume of the bilateral medial temporal lobe including the entorhinal cortex, head to tail of the hippocampus, and amygdala. (Matsuda et al., 2012). The stand-alone software program running on Windows for voxel-based morphometry analysis by statistical parametric mapping 8 (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) and the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL; Wellcome Department of Imaging Neuroscience) (Ashburner, 2007) were developed to differentiate patients with AD from healthy controls based on MRI data. First, MRI images were spatially normalized with only a 12-parameter affine transformation to the SPM template to correct for differences in brain size. These linearly transformed images were nonlinearly transformed and then modulated to the customized template for DARTEL, followed by smoothing using an 8-mm full width at half maximum Gaussian kernel. Each

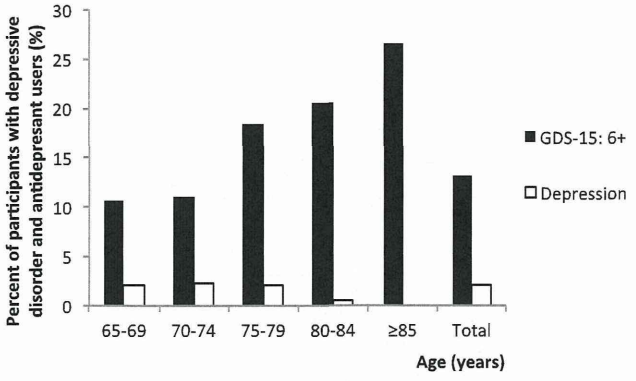

Fig. 1. Proportion of participants with depressive symptoms and depression.

participant's processed gray matter image was compared with the mean and SD of gray matter images of the 58 healthy volunteers chosen in the group comparison, using voxel-by-voxel z-score analysis with and without voxel normalization to global mean intensities (global normalization): Z-score = ([control mean] − [individual value])/(control SD). These Z-score maps were displayed by overlay on tomographic sections and surface rendering of the standardized brain (Matsuda et al., 2012).

2.6. Statistical analysis

Participants were divided into three groups: the 'no depressive symptoms' group (GDS-15 ≤ 5), the 'depressive symptoms' group (GDS-15 6+), and the 'depression' (depressive disorder) group. Analysis of variance (ANOVA) was used to compare potential correlates and GDS-15 scores among the three groups. ANOVA and analysis of covariance (ANCOVA) were used to determine the intergroup differences for the cognitive tests and BDNF measurements. Post-hoc analyses in ANCOVA were conducted using Bonferroni comparisons to compare cognitive tests among the groups. MRI measurements were compared using *t*-tests and ANCOVA. Ordinal logistic regression was used to study associations between the categories of depressive state ('no depressive symptoms', 'depressive symptoms', and 'depression') and cognitive performances, and serum BDNF. This analysis was not an analysis of risk factors since the data were collected in a cross-sectional fashion. Simple binary logistic regression was used to study associations the depressive symptoms ('depressive symptoms' versus 'no depressive symptoms') and brain volumes. Covariates such as significant variables of the potential correlates were included in the multivariate model. All statistical comparisons were made at the 0.05 level of significance, and all data management and statistical computations were performed using the IBM SPSS Statistics 20.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 4352 participants who completed all the assessments except the MRI scan, 3695 (85%) were defined as having 'no depressive symptoms' (GDS-15: ≤5 points), 570 (13%) fulfilled the criteria for 'depressive symptoms' (GDS-15: 6 + points), and 87 (2%) were diagnosed with depression. The proportion of participants with depressive symptoms increased with age: from 10.6% between the ages of 65 and 69 to 26.5% for subjects 85 years and older (Fig. 1). The mean GDS-15 scores in the 'no depressive symptoms', 'depressive symptoms', and 'depression' groups were 2.0 (SD = 1.5), 7.6 (SD = 1.81), and 4.2 (SD = 3.6), respectively ($p < 0.001$). There was a significant difference in age among the three groups ($p < 0.001$) (Table 1).

In comparisons with potential confounders, there were significant differences in education level ($p < 0.001$), living alone status ($p < 0.001$), walking speed ($p < 0.001$), frailty ($p < 0.001$), self-rated health ($p < 0.001$), regular exercise ($p < 0.001$), frequency of going outdoors ($p < 0.001$), and sleep time ($p = 0.018$) among the 'no depressive symptoms', 'depressive symptoms' and 'depression' groups (Table 1).

All cognitive performance measures including general function, memory, attention and executive function, and processing speed showed significant differences among the 'no depressive symptoms', 'depressive symptoms' and 'depression' groups by ANOVA. In multivariate analyses adjusted for significant correlates including age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time, significant effects were maintained in all cognitive tests except for the MMSE (Table 2). Post-hoc analyses revealed that the 'no depressive symptoms' group scored significantly better than the 'depressive symptoms' group in the word recall test and trail-making test part B. The story memory and symbol digit substitution tasks were scored higher by the 'no depressive symptoms' group compared with the 'depression' group (Table 2).

The mean BDNF concentrations were 21.2 ± 5.3 ng/ml in the 'no depressive symptoms' group, 20.2 ± 5.0 ng/ml in the 'depressive symptoms' group, and 20.3 ± 5.4 ng/ml in the 'depression' group ($p < 0.001$). The significant difference disappeared in multivariate analyses adjusted for the correlates.

Of the 618 participants who underwent an MRI scan, 544 (88%) were in the 'no depressive symptoms' group and 74 (12%) were in the 'depressive symptoms' group. The 'depressive symptoms' group

Table 2
Comparisons of cognitive performance among the groups.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics				
	Mean	SD	Mean	SD	Mean	SD	ANOVA *F*	*P*	ANCOVA *F*	*P*	Post hoc in ANCOVA
MMSE	26.5	2.4	26.1	2.5	26.6	2.6	10.285	<0.001	0.723	0.485	
Word recall	3.9	1.9	3.3	1.9	3.5	1.9	31.835	<0.001	9.901	<0.001	a
Story memory	6.9	1.8	6.4	1.9	6.4	1.9	20.134	<0.001	4.871	0.008	b
Trail-making test part A (s)	20.6	5.8	22.6	8.3	22.2	7.7	27.497	<0.001	3.424	0.033	
Trail-making test part B (s)	41.5	16.4	48.0	19.8	43.9	17.1	36.688	<0.001	5.600	0.004	a
Symbol digit substitution task	39.0	7.9	36.0	8.7	36.9	7.4	37.456	<0.001	4.252	0.014	b

a: $p < 0.05$ for comparison between the 'no depressive symptoms' and 'depressive symptoms' groups.
b: $p < 0.05$ for comparison between the 'no depressive symptoms' and 'depression' groups.
MMSE: mini-mental state examination. Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in ANCOVA.

Table 3
Comparisons of BDNF level, and hippocampal and whole gray matter atrophy.

	'No depressive symptoms' ($n = 3695$)		'Depressive symptoms' ($n = 570$)		'Depression' ($n = 87$)		Statistics			
	Mean	SD	Mean	SD	Mean	SD	ANOVA F	P	ANCOVA F	P
BDNF (ng/ml)	21.2	5.3	20.2	5.0	20.3	5.4	8.098	<0.001	2.738	0.065

	'No depressive symptoms' ($n = 544$)		'Depressive symptoms' ($n = 74$)		Statistics			
	Mean	SD	Mean	SD	t-test t	P	ANCOVA F	P
Bilateral MTL atrophy	0.7	0.5	0.8	0.6	1.753	0.083	3.197	0.074
Right MTL atrophy	0.7	0.6	0.9	0.7	2.229	0.028	5.169	0.023
Left MTL atrophy	0.6	0.5	0.7	0.5	0.054	0.957	0.007	0.933
Whole gray matter atrophy	2.0	1.4	2.2	1.2	1.530	0.126	0.999	0.318

BDNF: brain-derived neurotrophic factor, MTL: medial temporal lobe, Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in ANCOVA.

exhibited greater atrophy in right medial temporal lobe upon multivariate analyses ($p = 0.023$), although there were no significant differences in bilateral and left medial temporal lobe and whole gray matter atrophy (Table 3, Fig. 2).

The ordinal and binary logistic analyses examined the factors associated with being in 1 of 3 categories of depressive state ('depressive symptoms' vs. 'no depressive symptoms' and 'depression' vs. 'no depressive symptoms'). The likelihood of having the 'depressive symptoms' increased having low performances in word recall, story memory, and trail-making test part A and B, being low serum BDNF, and having high bilateral and right MTL atrophy. The correlates with 'depressive symptoms' that remained significant after adjustment were word recall, story memory, trail-making test part B, and right MTL atrophy (Table 4). The likelihood of having 'depression' increased having low performances in all cognitive tests, and being low serum BDNF. The correlates with 'depression' that remained significant after adjustment were word recall, story memory, trail-making test part A, and symbol digit substitution task (Table 4).

4. Discussion

The present study showed that depressive symptoms in older participants were associated with worse overall performance in tests of general cognitive function, memory, attention and executive functions, and processing speed. Similar results were observed when the data were controlled for socio-demographic, physiological, health, and behavioral variables.

Many studies have reported a relationship between depressive symptoms or major depression and cognitive dysfunction in older adults (Barnes et al., 2006; Berger et al., 1999; Devanand et al., 1996; Geerlings et al., 2000; Green et al., 2003; Verdelho et al., 2013; Wilson et al., 2002; Yaffe et al., 1999). The strengths of our study include a large sample size of rigorously assessed older people, and the potential to control for many variables implicated in cognition (age, education, marital status, health status, physical performance, and health-related behaviors). A new finding of our study was that, in the word recall test, story memory, and the trail-making tests, older adults with depressive symptoms achieved lower scores and took longer to complete the task than did people without depressive symptoms. In addition, word recall test, story memory, the trail-making test, and symbol digit substitution task scores were decreased in the depression group. These results suggest that memory, executive function, and processing speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms or depression.

We found that BDNF levels were significantly lower in the 'depressive symptoms' and 'depression' group than in the 'no depressive symptoms' group. Recently, Chu et al. compared the differences in BDNF levels among 167 Chinese older adults with

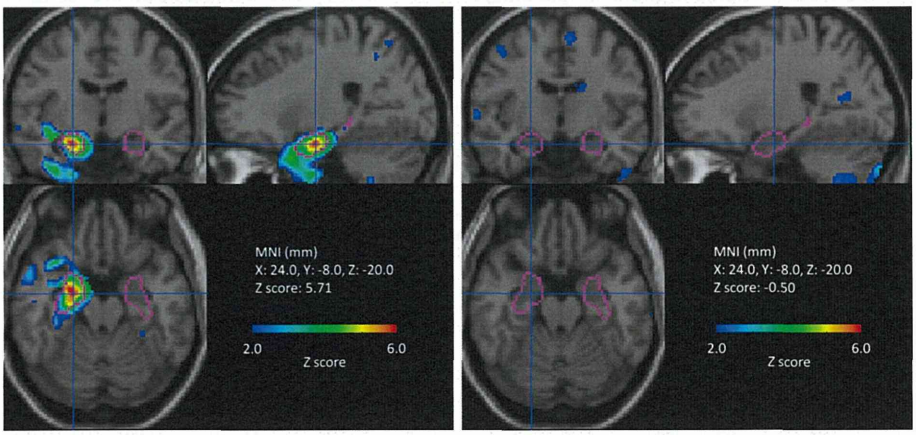

Fig. 2. Atrophy of the medial temporal lobe in participants with and without depressive symptoms. The panels show typical images, indicating regions of atrophy, in participants with and without depressive symptoms. The left panel shows whole brain cortical atrophy in a man (65 years old) with depressive symptoms. The Z-score of right medial temporal lobe atrophy was 3.8 in this depressive participant, who scored low on word recall (3 points) and had low serum BDNF levels (16.6 ng/ml). The right panel shows fusion images in a man (65 years old) without depressive symptoms. The Z-score of right medial temporal lobe atrophy was 0.2 in this non-depressive participant, who had a high word recall test score (5 points) and high serum BDNF levels (23.9 ng/ml).

Table 4
Relationships between 'Depressive symptoms' and 'Depression' and measurements.

	'Depressive symptoms' vs. 'No depressive symptoms'						'Depression' vs. 'No depressive symptoms'					
	Crude model			Adjusted model			Crude model			Adjusted model		
	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)	Beta	*P*	OR (95% CI)
MMSE	0.314	0.518	0.92 (0.89–0.95)	−0.024	0.244	0.98 (0.94–1.02)	−3.892	0.001	1.01 (0.92–1.10)	0.021	0.670	1.02 (0.93–1.12)
Word recall	−1.212	<0.001	0.83 (0.8–0.87)	−0.108	<0.001	0.90 (0.85–0.95)	−3.304	<0.001	0.89 (0.79–0.99)	−0.143	0.021	0.87 (0.77–0.98)
Story memory	−0.922	<0.001	0.87 (0.83–0.91)	−0.056	0.046	0.95 (0.90–1.00)	−2.913	<0.001	0.88 (0.79–0.99)	−0.150	0.018	0.86 (0.76–0.97)
Trail-making test part A	−2.778	<0.001	1.04 (1.03–1.06)	0.011	0.139	1.01 (1.0 0–1.03)	−4.518	<0.001	1.04 (1.01–1.07)	0.034	0.024	1.03 (1.00–1.07)
Trail-making test part B	−2.743	<0.001	1.02 (1.02–1.03)	0.009	0.004	1.01 (1.00–1.01)	−4.102	<0.001	1.01 (1.00–1.02)	0.009	0.194	1.01 (1.00–1.02)
Symbol digit substitution task	−0.131	0.53	0.96 (0.94–0.97)	−0.012	0.102	0.99 (0.97–1.00)	−2.495	<0.001	0.97 (0.94–0.99)	−0.042	0.011	0.96 (0.93–0.99)
BDNF	−1.184	<0.001	0.97 (0.95–0.98)	−0.018	0.043	0.98 (0.96–1.00)	−3.124	<0.001	0.97 (0.93–1.01)	−0.025	0.236	0.98 (0.94–1.02)
Bilateral MTL atrophy	0.442	0.036	1.56 (1.03–2.35)	0.480	0.069	1.62 (0.96–2.71)						
Right MTL atrophy	0.448	0.01	1.57 (1.11–2.20)	0.481	0.025	1.62 (1.06–2.47)						
Left MTL atrophy	0.014	0.957	1.01 (0.61–1.69)	0.067	0.829	1.07 (0.58–1.96)						
Whole gray matter atrophy	0.118	0.129	1.13 (0.97–1.31)	0.095	0.327	1.10 (0.91–1.33)						

Age, education level, living alone status, walking speed, frailty, self-rated health, regular exercise, frequency of going outdoors, and sleep time were included as covariates in the adjusted models.

major depression and those in a non-depressed control group. They found a significant negative association between age and BDNF levels and noted that BDNF was significantly lower in the major depression group than in the non-depressed control group (Chu et al., 2012). In a systematic review including 19 studies, BDNF levels were significantly higher in healthy people than in patients with depression (Brunoni et al., 2008). In addition, meta-regression found significant associations between BDNF levels and depression score changes (Brunoni et al., 2008). Our findings were similar to those of previous studies that found a negative association between BDNF levels and depression. Moreover, adjusted logistic model showed marginal significance in the relationship between serum BDNF and 'depressive symptoms' even though 'depression' was not associated with BDNF. It is possible that the small sample size in the 'depression' group, effects of antidepressant, (Nibuya et al., 1995) and multiple control variables in this study contributed to the non-significant results.

Atrophy of the right medial temporal lobe in the 'depressive symptoms' group was higher than that in the 'no depressive symptoms' group even in multivariate analyses. BDNF supports cholinergic, dopaminergic, serotonergic, and neuropeptide-containing neurons (Hyman et al., 1991; Knusel et al., 1991; Mamounas et al., 1995) and may play an important role in AD and depression-related pathophysiology. Several studies have shown that serum BDNF levels are reduced in depressed patients and can be normalized by treatment (Karege et al., 2005; Monteleone et al., 2008; Sen et al., 2008). Erickson and colleagues reviewed the interactions between exercise, depression, and hippocampal function including memory and atrophy and concluded that there was mounting evidence that BDNF expression plays an important role in age-related hippocampal atrophy and that geriatric depression magnifies hippocampal atrophy (Erickson et al., 2012). BDNF is highly concentrated in the hippocampus (Phillips et al., 1990; Wetmore et al., 1990), promoting cell proliferation and signaling through several pathways. A single nucleotide polymorphism in the *BDNF* gene causes a valine (val) to methionine (met) substitution at codon 66 in the prodomain (Egan et al., 2003). BDNF val66met affects the regulated secretion of BDNF in the hippocampus (Egan et al., 2003) and has been related to lower serum levels of BDNF (Ozan et al., 2010) and smaller hippocampal volumes (Pezawas et al., 2004; Szeszko et al., 2005), which can lead to deficits in executive function (Frodl et al., 2006) and memory function (Erickson et al., 2009). Moreover, hippocampal volume is consistently reduced in BDNF met carriers compared with BDNF val/val patients with major depressive disorder (Frodl et al., 2007). The memory task engaged the right hippocampal region when the memory task was compared with either the baseline or the priming condition (Squire et al., 1992). The relationships between cognitive decline, low BDNF, and atrophy of the right medial temporal lobe were confirmed in this study, in accordance with previous studies.

Although this study is a large population-based sample of older adults, causation cannot be inferred from a cross-sectional study. Further prospective investigations are needed to validate the causal relationships between cognitive decline and depressive symptoms in older people. Moreover, our study excluded individuals with neurological disorders such as stroke and Parkinson's disease and those who were certified to have long-term care insurance needs because of functional decline. Hence, our findings may not be generalizable to these patient populations.

Nevertheless, this study provides promising preliminary evidence that memory, executive function, and cognitive speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms or depression. Serum BDNF concentration and atrophy of the right medial temporal lobe may play a role as mediators. Further investigation is needed, and future research should include a prospective measurement of cognitive decline to establish the validity of these preliminary results.

Contributors

Author contributions were as follows: Hiroyuki Shimada, Takao Suzuki: study concept and design and data analysis or interpretation; Hiroyuki Shimada, Hyuntae Park, Hyuma Makizako, Takehiko Doi, Sangyoon Lee, Takao Suzuki: drafting or revising the manuscript for important intellectual content. All authors contributed to and have approved the final manuscript.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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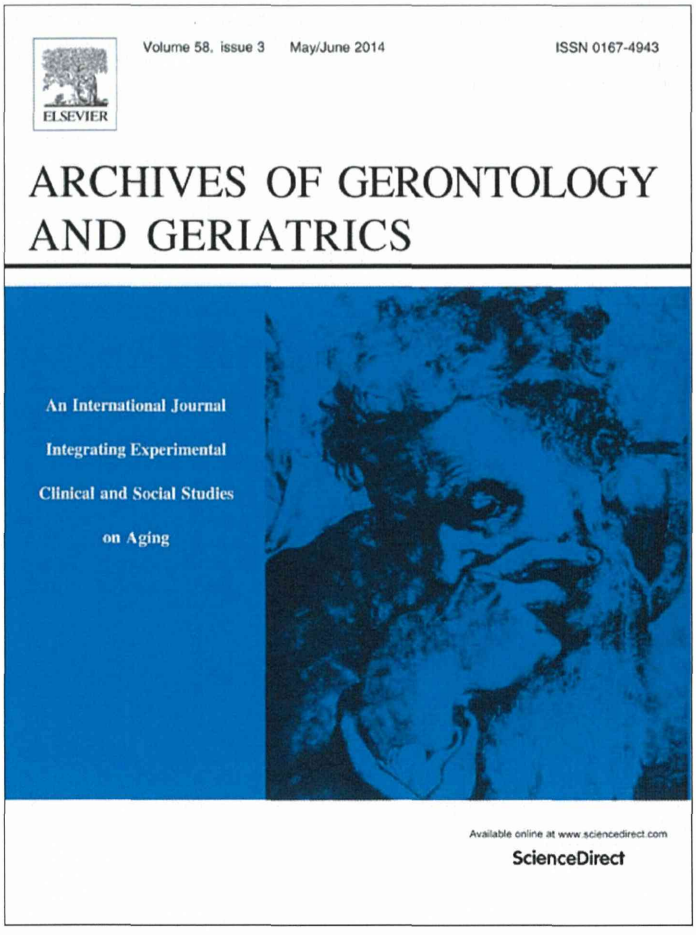

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The combined status of physical performance and depressive symptoms is strongly associated with a history of falling in community-dwelling elderly: Cross-sectional findings from the Obu Study of Health Promotion for the Elderly (OSHPE)

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ABSTRACT

The purpose of this study was to examine whether the combined factors of physical performance, depressive symptoms and cognitive status are significantly associated with a history of falling in community-dwelling elderly. We performed a cross-sectional community-based survey, the OSHPE, from August 2011 to February 2012. In total, 5104 community-dwelling older adults aged 65 years and older (mean age 72.0) participated in the OSHPE. Participants underwent a grip strength (GS) test, chair stand test (CST), Timed Up & Go (TUG) test, Geriatric Depression Scale (GDS), and Mini-Mental State Examination (MMSE). Of the 4481 participants who met our requirements, 645 (14.4%) participants reported falling at least once in the past year. In a signal detection analysis (SDA), we found that the combination of GDS (≥6 points) and TUG (≥10.6 s) had the highest fall rate (36.4%), and the combination of GDS (<6 points) and CST (<11.1 s) had the lowest fall rate (11.7%). The highest fall rate group had a significantly higher odds ratio (OR) compared with the lowest fall rate group after adjusting for other potentially confounding variables [OR 3.12 (95% confidence interval (CI) 2.08–4.68) $p < 0.001$]. The combination of depressive symptoms, TUG, and CST performance was strongly associated with a history of falling in community-dwelling elderly.

1. Introduction

Falls, fall-related fractures, and fear of falling are a major cause of public health problems and common causes of long-term care enrollment in older populations (Gillespie & Friedman, 2007; Masud & Morris, 2001). There are many distinct causes of falls in older people. Fall risk factors are frequently classified as intrinsic (e.g., physical frailty and sensory deficits) or extrinsic (e.g., home hazards and footwear) factors (Fabre, Ellis, Kosma, & Wood, 2010).

Guidelines for the prevention of falls in older persons compiled by the Panel on Falls Prevention of the American and British Geriatrics Society identified the major fall risk factors and their relative importance (2001). One of the strongest risk factor domains is muscle weakness and problems with gait and balance. These are key risk factors for falls and present with high OR (values ranging from 3.0 to 4.9) (Rubenstein, 2006).

One of the complications of falls in older people is the post-fall anxiety syndrome; an older individual refrains from activity because of fear of falling. Falls in older people are associated not only with physical functions such as muscle weakness, balance impairment, and gait dysfunction (Masud & Morris, 2001), but also psychological factors, e.g., depressive symptoms (Somadder, Mondal, Kersh, & Abdelhafiz, 2007). A higher prevalence of depression has been reported in fallers than in non-fallers (Wada et al., 2008), and depressive symptoms have been shown to be a

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risk factor for falls among older people (Anstey, Burns, von Sanden, & Luszcz, 2008; Deandrea et al., 2010; Kwan, Lin, Close, & Lord, 2012). Additionally, the risk of falls is proportional to the number itself of fall-related risk factors (Tinetti, Williams, & Mayewski, 1986). Previous studies suggest that the combined status of declining physical functions and psychological status such as depression may be related to falling. However, little studies have reported that which combination of modifiable factors has most impact for falling and its optimal cut-off points are unclear.

Measures of lower extremity function, balance, and gait performance have been recommended as a screening for fall risk in older people (Rubenstein & Josephson, 2006; Scott, Votova, Scanlan, & Close, 2007; Shimada et al., 2009). Previous studies using instruments of physical function assessment as related to falls have provided potential cut-off scores to identify increased fall risks among community-dwelling older people (Fabre et al., 2010; Scott et al., 2007). For instance, the TUG test is a relatively simple screening test and a specific indicator of whether falls are likely to occur in older adults. A previous study indicated that a cut-off time of 10–12 s separated fallers from non-fallers in a group of community-dwelling older adults (Trueblood, Hodson-Chennault, McCubbin, & Youngclarke, 2001). In another study, community-dwelling older adults who took 13.5 s or longer to perform the TUG were classified as fallers with an overall correct prediction rate of 90% (Shumway-Cook, Brauer, & Woollacott, 2000). These studies demonstrate differences in the cut-off points for falling risk. One reason for these different cut-off points may be a limited sample size. Furthermore, even though there studies focused on community-dwelling older people, the participant characteristics were different (e.g., physical function and psychological status). Therefore, the combined status of risk for falling should be considered to identify risks for falls in a large population-based study. Such information would be useful because factors related to falls may be different in older people with or without depressive symptoms.

The aim of this study was to examine which combination of modifiable factors, such as physical performance, depressive symptoms, and cognitive status were closely associated with a history of falling in community-dwelling elderly. This investigation may be critical to the exploration of the combined classification of modifiable factors for fall risk screenings, in order to develop future risk assessments and prevention programs.

2. Participants and methods

2.1. Participants

We performed a cohort study entitled OSHPE (Shimada et al., 2013) from August 2011 to February in 2012. Individuals selected for participation in the OSHPE were chosen from the 15,974 older people living in Obu, Japan. Inclusion criteria required that the participant was aged 65 years or older at the time of examination in 2011 or 2012, and living in Obu. Prior to recruitment, we excluded 1661 individuals who had participated in another study, needed hospitalization or residential care, and required support or care by the Japanese public long term care insurance system (Care Level $\geq$ 3/5). Recruitment involved sending mail messages to 14,313 people; 5104 people underwent a health check. We excluded participants who reported a history of stroke, Parkinson's disease, Alzheimer's disease, other serious neurologic diagnoses, and those who could not complete the physical performance tests. Finally, 4481 participants (mean age 72.0) were included in the present study, and their data were analyzed. Informed consent was obtained from all participants prior to their inclusion in the study. The Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

2.2. Fall interview

Fall history was assessed using face-to-face interviews. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" (Lamb, Jorstad-Stein, Hauer, & Becker, 2005). The question "Do you have any history of a fall within the past year?" was used for detecting fallers. Participants who answered yes to the question were considered to be fallers (Wada et al., 2008).

2.3. Measurement of depressive symptoms

The 15-item GDS was administered to assess presence depressive symptoms (Yesavage, 1988). The GDS is unique because it was specifically developed for use in geriatric patients, and it contains fewer somatic items. The participants were required to respond to each question with only a "yes" or "no". The sum of GDS scores ranges from 0 to 15; higher scores indicate a greater likelihood of depression in an older adult.

2.4. Physical and cognitive assessments

The following physical performance tests were conducted: GS, CST (Hirsch et al., 1997), and the TUG (Podsiadlo & Richardson, 1991). All physical performance tests were performed by licensed and well-trained physical therapists. The MMSE (Folstein, Folstein, & McHugh, 1975), administered by well-trained examiners, assessed global cognitive function. GS was measured in kilograms with participants' dominant hand using a portable grip strength dynamometer (GRIP-D; Takei Ltd., Niigata, Japan). The measurement was taken once and in the standing position. CST involved standing up and sitting down five times from a sitting position as quickly as possible (Hirsch et al., 1997). In CST, physical therapists recorded the time needed to perform five consecutive chair-stands (timed to 0.1 s) from a seated position on a 45-cm tall chair, with arms folded across the chest. General mobility was assessed using the TUG. TUG involves the participant rising from a standard armchair, walking a distance of 3 m at a normal and safe pace, turning around, walking back to the chair and sitting down again (Podsiadlo & Richardson, 1991). TUG is measured in seconds using a stopwatch. The time taken to complete TUG was measured twice and the best-timed trial was used for each participant's score.

2.5. Statistical analysis

Student's *t* test for differences in means and chi-square tests for differences in proportions were used to compare group differences in characteristics between the faller and non-faller groups. The SDA determined, through creation of a decision tree, the most sensitive and specific algorithm to categorize subgroups with a shared association with a history of falling. The SDA was performed with ROC4 software (Department of Veterans Affairs, Mental Illness Research, Education, and Clinical Centers, 2002) including GS, CST, TUG, GDS, and MMSE as independent variables. The merits of SDA have been summarized in a previous article (Agras et al., 2000). SDA is a form of recursive partitioning that considers at each step all possible predictors (at every possible cut point), with the optimal predictor and optimal cut point chosen in terms of their sensitivity and specificity. The cut point was set in advance because no optimal predictor was associated with an outcome at $p < 0.01$. Furthermore, simple (univariate) and multiple (multivariate) logistic regression analyses were per-