activity are important risk factors for dementia, it is unclear how the interactions between these two factors affect the development of cognitive impairment.

Previous cohort studies examining the effects of *APOE* genotype and physical activity on the risk of dementia and AD assessed physical activity levels using self-reported questionnaires [21,22]. In the current study, we monitored physical activity levels using portable triaxial accelerometers and provided objective data of physical activity levels, including whether the activity reached the recommended levels (≥150 minutes at ≥3.0 METs per week). Our findings suggested that the associations between moderate-intensity physical activity behavior and cognitive function might be more remarkable in MCI subjects carrying *APOE* ε4. Habitual moderate-intensity physical activity at the recommended levels (≥150 minutes per a week) seems to be not only beneficial for physical health but also provides cognitive protection in older people [23]. Furthermore, our data indicated that this level of moderate-intensity physical activity might help maintain cognitive functions even in older adults with increased risks for dementia, such as those with MCI or those carrying the *APOE* ε4 allele.

However, our data was collected by a cross-sectional design. Therefore, longitudinal studies and clinical trials are needed to understand the temporal direction of associations among moderate-intensity physical activity, cognition, and *APOE* genotype in older adults with MCI. In addition, investigations on healthy individuals and subjects with AD are needed to clarify the effects of the *APOE* ε4 allele and objectively determined physical activity levels on AD-related pathology.

CONCLUSION

In summary, this study found that low levels of moderate-intensity physical activity are associated with poor cognitive functions, especially memory and language functions, in subjects with MCI who are *APOE* ε4 carriers. Our findings imply that a habitual physical activity for ≥150 minutes per week at an intensity of ≥3 METs may have a greater impact on cognitive functioning among subjects with MCI who are *APOE* ε4 carriers compared to those who are non-carriers.

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Depressive symptoms and cognitive performance in older adults

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ABSTRACT

Many longitudinal studies have found that older adults with depressive symptoms or depression have increased risk of cognitive impairment. We investigated the relationships between depressive symptoms or depression, cognitive function, serum brain-derived neurotrophic factor (BDNF), and volumetric MRI measurements in older adults. A total of 4352 individuals aged 65 years or older (mean age 72 years) participated in the study. We investigated medical history and geriatric depression scale-15 (GDS-15) items to determine depression and depressive symptoms. Cognitive tests included the mini-mental state examination (MMSE), story memory, word list memory, trail-making tests, and the symbol digit substitution task. Of the 4352 participants, 570 (13%) fulfilled the criteria for depressive symptoms (GDS-15: 6 + points) and 87 (2%) were diagnosed with depression. All cognitive tests showed significant differences between the 'no depressive symptoms', 'depressive symptoms', and 'depression' groups. The 'depressive symptoms' and 'depression' groups showed lower serum BDNF ($p < 0.001$) concentrations than the 'no depressive symptoms' group. The 'depressive symptoms' group exhibited greater atrophy of the right medial temporal lobe than did the 'no depressive symptoms' group ($p = 0.023$). These results suggest that memory, executive function, and processing speed examinations are useful to identify cognitive decline in older adults who have depressive symptoms and depression. Serum BDNF concentration and atrophy of the right medial temporal lobe may in part mediate the relationships between depressive symptoms and cognitive decline.

1. Introduction

An epidemiological study estimated that up to half of Alzheimer's disease (AD) cases worldwide (17.2 million) might be attributable to potentially modifiable risk factors. If the prevalence of all these risk factors were 10% lower, it is estimated that there would be as many as 1.1 million fewer AD cases worldwide; if risk factor prevalence were 25% lower, AD prevalence could potentially be reduced by over 3.0 million cases worldwide (Barnes and Yaffe, 2011).

Persons with cognitive decline are at increased risk for progressing to mild cognitive impairment (MCI) and dementia. Findings from numerous epidemiologic and clinical studies suggest that multiple biological, behavioral, psychosocial, and environmental factors may contribute to the risk of cognitive decline (Plassman et al., 2010). Also, many longitudinal studies have found that older persons with depressive symptoms or depression have an increased risk of cognitive decline, MCI, and dementia (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). In fact, depressive symptoms are common in dementia patients, with a prevalence of approximately 30% in people with dementia (Lyketsos et al., 2002). It is important to clarify which cognitive domains are associated with depressive symptoms or depression and to identify potential mediators between depression and cognitive decline to design strategies for the prevention of dementia in older adults.

Previous studies have reported that serum brain-derived neurotrophic factor (BDNF) levels are reduced in major depressive disorder and depressive symptoms (Cunha et al., 2006; Karege et al., 2002; Shimizu et al., 2003; Terracciano et al., 2011). BDNF has neurotrophic and neuroprotective properties (Barde, 1994; Lindvall et al., 1994) and can affect functions that underlie brain plasticity (Altar and DiStefano, 1998; Lu and Chow, 1999; McAllister

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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

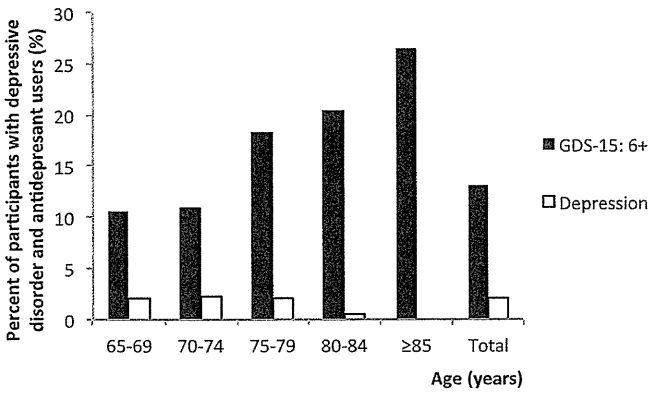

Fig. 1. Proportion of participants with depressive symptoms and depression.

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

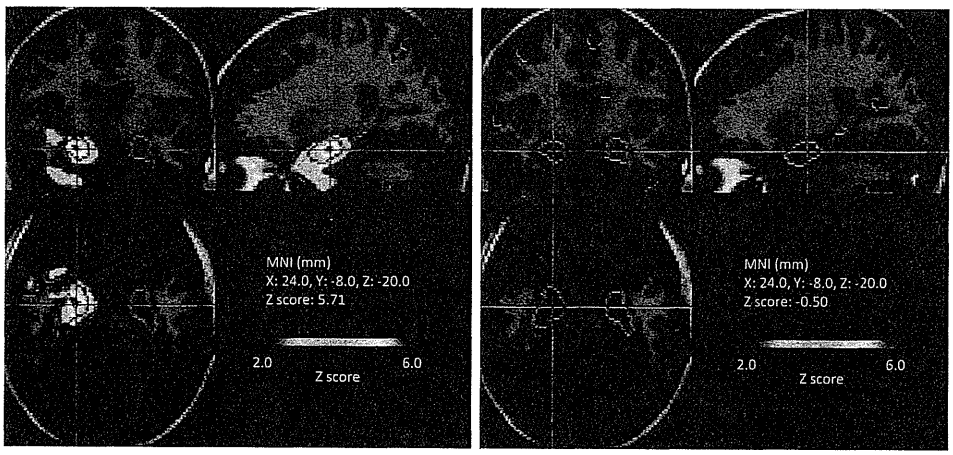

Fig. 2. Atrophy of the medial temporal lobe in participants with and without depressive symptoms. The panels show typical images, indicating regions of atrophy, in participants with and without depressive symptoms. The left panel shows whole brain cortical atrophy in a man (65 years old) with depressive 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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The funding source played no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Effects of mild and global cognitive impairment on the prevalence of fear of falling in community-dwelling older adults

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ABSTRACT

Objectives: Few studies have reported the relationship between fear of falling (FoF) and mild and global cognitive impairment in community-dwelling older adults. We aimed to determine whether the status of cognitive impairment affects the prevalence of FoF in community-dwelling older adults.
Study design: Cross-sectional study among 4474 community-dwelling older adults who participated in the Obu Study of Health Promotion for the Elderly.
Main outcome measures: Participants underwent cognitive tests and were divided into three groups: cognitive healthy, mild cognitive impairment (MCI), and global cognitive impairment (GCI). FoF and related variables, such as fall history, physical function, and depression, were also investigated.
Results: The prevalence of FoF was significantly different by group ($p < 0.001$; healthy: 43.6%, MCI: 50.6%, GCI: 40.6%). Logistic regression analysis showed that GCI (odds ratio = 0.63; 95% confidence interval = 0.526–0.76) was independently associated with FoF, after controlling for confounding factors. Older adults with GCI showed the lowest prevalence of FoF, although they had the lowest physical function comparing with the other groups ($p < 0.001$).
Conclusion: MCI and GCI in community-dwelling older adults affect the prevalence of FoF in a completely different manner. Further study is required to determine whether insensitivity to FoF with GCI increases the risk of falling in older adults.

1. Introduction

Fear of falling (FoF) is defined as "a lasting concern about falling that leads to an individual avoiding activities that he/she remains capable of performing" [1]. The main consequences of FoF are an increased risk for falling, restriction and avoidance of activities, and ultimately, deteriorated physical and mental performance, as well as decreased quality of life [2]. The prevalence of FoF ranges from 33% to 85%, being higher in women than in men, and increases with age [3,4]. FoF is associated with a history of falls, gait speed, use of walking aids, polypharmacy, and depression [5,6]. In spite of a number of reports regarding various factors associated with FoF, few studies have examined the relationship between FoF and cognitive decline, although it is almost universal in the general elderly population and increases with age [7].

Cognitive impairment, such as impairment of global cognition and executive function, contributes to the deterioration in the ability to carry out tasks in activities of daily living (ADL) [8,9]. Additionally, these cognitive impairments have been identified as a fall risk factor in clinical practice guidelines [10]. FoF also has been recognized as an important psychological factor associated with accidental falls and restricting everyday functioning [11]. However, whether the prevalence of FoF is affected according to the severity

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of cognitive impairment is still unclear. In addition to studying the risk of falling, investigation of FoF may be important in medical management of older adults with cognitive impairment.

Although many studies have reported that global cognitive impairment (GCI) confers a moderate to high risk of serious fall-related injury [10], recent evidence indicates that even mild cognitive impairment (MCI) is a risk factor for falls [12]. MCI is conceptualized to be the earliest feature of cognitive disorders and a prodromal condition between normal and dementia [13]. We have previously reported that memory decline is associated with a lower prevalence of FoF among older adults [14]. However, the sample size of our previous study was relatively small ($n = 101$) and the variety of cognitive impairments (i.e. MCI and GCI) was not considered in that study.

Therefore, the purpose of this study was to examine the effects of severity of cognitive impairment on the prevalence of FoF in a larger cohort of community-dwelling older adults. We hypothesized that mild and global cognitive impairment influence the prevalence of FoF in a different manner because of a difference in the nature of cognitive deficits.

2. Methods

2.1. Participants

We performed a cohort study "Obu Study of Health Promotion for the Elderly" (OSHPE) from August in 2011 to February in 2012. Enrollment in the OSHPE was available to 15,974 older people living in Obu, Japan. Inclusion criteria required that participants lived in Obu and were aged 65 years or older at examination in 2011 or 2012. Before recruitment, 1661 people were excluded because they had participated in another study, required hospitalization or residential care, or were certified as requiring more than level 3 care, requiring support or care by the Japanese public long-term care insurance (LTCI) system. Recruitment was conducted by mail sent to 14,313 people and 5104 people underwent a health check. A total of 4474 subjects satisfied the inclusion criteria and conducted all assessments. The inclusion criterion in this study was persons not certified as any grade requiring support or care by the Japanese public LTCI system. The participants were classified into three groups: cognitive healthy ($n = 2735$; mean age ± standard deviation [SD], 71.3 ± 5.1 years), MCI ($n = 938$; age ± SD = 71.9 ± 5.5 years) and GCI ($n = 801$; age, $M = 74.4 \pm 6.2$ years). GCI was defined as a deficit in general cognitive function; the Mini-Mental State Examination (MMSE) score was 23 or lower [15]. The criteria of MCI were those described by Petersen [13]. These criteria involved the following: (1) having subjective memory complaint, (2) having objective cognitive decline, (3) intact general cognitive function; MMSE score >23 [15], (4) absent from of clinical criteria for dementia, and (5) independent in ADL. Objective cognitive decline was defined as a lower cognitive function in multiple domains more than 1.5 SD from the healthy database. Cognitive functions in multiple domains were assessed using the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT). NCGG-FAT contains cognitive battery tests and the contents of measurement were described in detail in a previous study [16]. The battery consists of eight tasks to assess memory, attention and execution, processing speed, and visuospatial skill. The term "cognitive healthy" in this study was defined as having intact cognitive ability, and not having objective cognitive impairment. Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

2.2. FoF/fall history

FoF and fall history was assessed by face-to-face interview with participants. FoF was assessed by a fourth-ordered choice, closed-ended question about participants' general FoF. The question was phrased as follows: "Are you afraid of falling?" Participants who responded "very much" or "somewhat" were assigned to the fear group. Participants who responded "a little" or "not at all" were assigned to the no-fear group [14,17], which has a high test–retest reliability [18]. The question "Do you have any history of a fall within the past year?" was used for detecting fall. A fall was defined as "an unexpected event in which the person comes to rest on the ground, floor, or lower level" [19]. Falls resulting from extraordinary environmental factors (e.g. traffic accidents or falls while riding a bicycle) were excluded. On the basis of their fall history, participants were classified as fallers if they fell twice or more times within the past year [20].

2.3. Potential correlates with FoF

Demographic data were recorded, including age, gender, and educational history. Participants completed a questionnaire on medical condition, including current medications and lifestyle. The medical questionnaire found a variety of diseases (hypertension, heart disease, stroke, and diabetes mellitus) and total medication used administered by a nurse. Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS) [21].

The timed up & go test (TUG) was used to assess physical performance [22]. The TUG involves rising from a chair, walking 3 meters, turning around, walking back to the chair, and sitting down. Participants were instructed to complete the task at their usual walking pace. The score for this test represents the time (in seconds) that the participant needed to complete the assessment. Lower times indicate better physical performance. Participants were also asked about their use of walking aids in daily life.

2.4. Statistical analysis

One-way analysis of variance (ANOVA) was used to test differences between groups. When a significant main effect was found from these analyses, the Bonferroni post hoc test was employed was performed to determine differences between pairs of means. The Chi-square test was used to test differences in proportions between groups.

When there is a large number of cell sizes for some of the cross-tabulations, it can be difficult to determine which groups have significant differences within the analyses. Therefore, standardized adjusted residuals were calculated for each of the cells to determine which cell differences contributed to the Chi-square test results. Cells with significant standardized adjusted residuals (>±1.96) are indicated by underlining their percentages in the tables [23,24].

Logistic regression analysis, performed as a stepwise analysis, was carried out to examine whether the classification schema based on cognitive function was independently associated with FoF. In this analysis, the presence or absence of FoF was used as the dependent variable (no-fear = 0, fear = 1). Individual group classification was entered as dichotomous categorical variables (fitting into that group = 1; others = 0). Other independent variables also included possible confounders were age, gender, educational history, TUG, use of walking aids, GDS, and medications. Gender, fall history, and use of walking aids were created as categorical variables (male = 0, female = 1; non-faller = 0, faller = 1; non-user = 0, user = 1). All analyses were performed using commercially available software, IBM SPSS statistics software (Version 20; IBM Corp., Chicago). Statistical significance was set at $p < 0.05$ a priori.

Table 1
Demographic characteristics, and health outcomes of the groups.

	Cognitive healthy (n=2735)	MCI (n=938)	GCI (n=801)	p-Value
Age (years)	71.3±5.1	71.9±5.5††	74.4±6.2$^{\$\$,**}$	<0.001
Gender (males)	1298 (47.5)	451 (48.1)	325 (60.3)	<0.001[a]
Educational history (years)	11.9±2.5	10.9±2.4††	10.3±2.5	<0.001
MMSE (points)	27.4±1.8	26.6±1.8††	21.6±1.8$^{\$\$,**}$	<0.001
Fear of falling	1193 (43.6)	475 (50.6)	325 (40.6)	<0.001[a]
Fall history (fallers)	110 (4.0)	67 (7.1)	48 (6.0)	<0.001[a]
Medical illness (%)				
Hypertension	1237 (45.2)	464 (49.5)	395 (49.3)	<0.001[a]
Heart disease	443 (16.2)	193 (20.6)	128 (15.9)	0.006[a]
Stroke	98 (3.6)	61 (6.5)	64 (7.9)	<0.001[a]
Diabetes mellitus	362 (13.2)	138 (14.7)	102 (12.7)	0.41[a]
TUG (s)	8.1±1.5	8.6±2.3††	9.2±3.2$^{\$\$,**}$	<0.001
Walking aids use	60 (2.2)	37 (4.0)	67 (8.4)	<0.001[a]
GDS (points)	2.6±2.5	3.4±2.7††	3.4±2.8$^{\$\$,**}$	<0.001
Total number of medication doses	1.9±2.1	2.3±2.2††	2.2±2.2**	<0.001

Underlined %=cells with significant adjusted standardized residuals; MMSE: Mini-Mental State Examination; TUG: timed up & go test; GDS: Geriatric Depression Scale.
[a] Values are means±SD or n (%). All p-values were generated from one-way ANOVA or Chi-square.
†† Significant difference between cognitive healthy and MCI (Bonferroni test, $p<0.01$).
** Significant difference between cognitive healthy and GCI (Bonferroni test, $p<0.01$).
$^{\$\$}$ Significant difference between MCI and GCI (Bonferroni test, $p<0.01$).

3. Results

The characteristics in participants and comparison between groups are summarized in Table 1. Cognitive healthy participants were significantly younger, had a higher educational history, higher MMSE, faster TUG, lower rate of walking aids use, GDS, and number of medications than those with MCI and GCI ($p<0.001$). Participants with GCI were significantly older, had a lower educational history, lower MMSE, slower TUG, and a higher rate of walking aid use than the other groups ($p<0.001$). The rate of males was significantly different by group ($p<0.001$; healthy: 47.5%, MCI: 48.1%, GCI: 60.3%). The prevalence of FoF was significantly different by group ($p<0.001$; healthy: 43.6%, MCI: 50.6%, GCI: 40.6%). Participants with MCI showed the highest prevalence of FoF (standardized adjusted residuals=4.2), while those with GCI showed the lowest prevalence of FoF (standardized adjusted residuals=−2.5). The prevalence of fallers was significantly different by group ($p<0.001$; healthy: 4.0%, MCI: 7.1%, GCI: 6.0%). Participants with MCI showed the highest prevalence of fallers (standardized adjusted residuals=3.3), while cognitive healthy participants showed the lowest prevalence of fallers (standardized adjusted residuals=−3.9).

Logistic regression analysis showed that classification to GCI (odds ratio [OR]=0.63; 95% confidence interval [CI]=0.53–0.76; $p<0.001$) was independently associated with FoF accounting for the following confounding factors: age (OR=1.03; 95% CI=1.02–1.05; $p<0.001$), gender (OR=0.28; 95% CI=0.25–0.32; $p<0.001$), educational history (OR=0.96; 95% CI=0.93–0.99; $p=0.003$), TUG (OR=1.1; 95% CI=1.06–1.16; $p<0.001$), use of walking aids (OR=2.07; 95% CI=1.33–3.23; $p<0.001$), GDS (OR=1.16; 95% CI=1.13–1.19; $p<0.001$), and number of medications (OR=1.08; 95% CI=1.04–1.12; $p<0.001$). Fall history, and classification to cognitive healthy and MCI did not show a significant relationship. The model was well calibrated between declines of observed and expected risk (Hosmer–Lemeshow $\chi^2=8.0$, $p=0.44$) (Table 2).

4. Discussion

This is the first study to clarify the effect of cognitive impairment, by dividing participants into several groups based on cognitive performance, on the prevalence of FoF in community-dwelling older adults. The present study found that MCI and GCI in community-dwelling older adults affect the prevalence of FoF in a completely different manner; the prevalence of FoF was highest with MCI and lowest with GCI. Furthermore, GCI was independently associated with a lower prevalence of FoF, even after accounting for confounding factors, such as demographic, physical, and mental factors.

Subjects with GCI might have underestimated their functional deficits and disregarded their risk of falling because they had the lowest prevalence of FoF, despite having the lowest physical function (i.e. slowest TUG and highest rate of users with walking aids). Older adults with dementia are often unable to appreciate or recognize their own deficiencies in motor, behavioral or cognitive functioning, which are evident to clinicians and caregivers [25]. This condition is regarded as "anosognosia" and is described as lack of awareness of impairments in ADL or of neuropsychological deficits [26], particularly in patients with Alzheimer's disease [27]. This impaired awareness is significantly correlated with the severity of global cognitive impairment, as assessed by the MMSE [28]. Therefore, GCI may contribute to insensitivity to FoF and be more likely to lead to adopting dangerous behaviors, and is likely to be observed in Alzheimer's disease [27].

Subjects with MCI had a higher prevalence of FoF and fallers than the cognitive healthy subjects and lower physical function than them. This is in line with a previous study, which found that MCI increases the risk of falling in older adults [12]. Anosognosia (i.e. lack of awareness) is frequent in patients with Alzheimer's

Table 2
Factors associated with FoF in stepwise logistic regression.

Factor	OR	95% CI	p-Value
Age	1.03	1.02–1.05	<0.001
Gender	0.28	0.25–0.32	<0.001
Educational history	0.96	0.93–0.99	0.003
TUG	1.1	1.06–1.16	<0.001
Walking aids usage	2.07	1.33–3.23	0.001
GDS	1.16	1.13–1.19	<0.001
No. of medication	1.08	1.04–1.12	<0.001
GCI	0.63	0.53–0.76	<0.001
Cognitive healthy	–	–	0.26
MCI	–	–	0.26
MMSE	–	–	0.99
Fall history	–	–	0.06

FoF, fear of falling; TUG, timed up & go test; GDS, Geriatric Depression Scale; GCI, global cognitive impairment; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

disease but not in those with MCI [25,29]. However, having anxiety is the most frequent behavioral symptom in MCI subjects [30]. Fall experience, decreased physical function, and feeling anxiety may contribute to the increased prevalence of FoF in MCI subjects. Therefore, the feeling of FoF may depend on the severity of cognitive impairment, and there may have been prevalent differences between the MCI and GCI groups in the present study.

GCI has been reported as a major risk factor of fall and serious fall-related injury [10]. GCI subjects might be unable to recognize their risks of falling and select a safety strategy during ambulation and transfer, despite having decreased physical function. This insensitivity to FoF may be one of the characteristics of psychological changes in older adults with GCI and account for an increased risk of falling derived from GCI. However, the design of the current study, as with other cross sectional studies, limits the interpretation of the results with regard to causality between FoF and associated factors. A longitudinal study is necessary to examine whether the insensitivity to FoF in GCI subjects who have decreased physical function leads to an increased incidence of accidental falls. If this hypothesis is verified, education and an exercise program specifically designed to address the cognitive needs and insensitivity to FoF among participants with GCI may be beneficial for preventing falls.

Another limitation of this study is the sub-optimal use of the single-item FoF measure. Further study is needed to examine the relationship between cognitive impairment and fear of falling during various activities of daily living using measures of falls efficacy which has been validated in older people with cognitive impairment [31,32]. However, as it is reported that single item FoF measurement shows good correlation with the Fall Efficacy Scale-International [33], a single question regarding FoF has been found to have high validity with continuous measures of FoF [34]. Thus, we consider that the relevance of our research is not lost by the way of FoF measurement. Finally, the incidence of falling in our subjects was relatively low compared with that in other studies [35], while a recent systematic review estimated that the incidence of falls among older people ranged from 14.7% to 34% [36]. Additionally, Milat and colleague [37] reported that older adults who fell more than twice were only 9.9% of all participants. These differences may be due to differences between races and/or physical function status of the participants. The findings of the present study differ from available comparable studies in which fall history was associated with FoF [5,6]. However, Austin and colleague [3] also reported that fall history was not found to predict FoF. Like this previous study, low rate of fall incidence might have weakened any relationship between falls and FoF. The strengths of the present study include its much larger sample size and that it is the first study to clarify the significant difference in prevalence of FoF between cognitive statuses which were classified strictly based on objective assessment measures.

5. Conclusion

Older adults with GCI have lower prevalence of FoF despite having lower physical function. GCI is independently associated with a lower prevalence of FoF while accounting for confounding factors, such as demographic, physical, and mental factors. However, MCI subjects have a higher prevalence of FoF and fallers than those with GCI and cognitive healthy subjects. GCI may induce disparity between awareness and function, which leads to insensitivity to FoF. Further study is required to determine whether insensitivity to FoF with GCI induces the risk of falling in older adults.

Contributors

Kazuki Uemura, Hiroyuki Shimada, Hyuma Makizako and Takehiko Doi were responsible for study concept and design; Takao Suzuki and Hyuntae Park contributed to study supervision and funding; Kota Tsutsumimoto, Daisuke Yoshida, Yuya Anan, Tadashi Ito and Sangyoon Lee contributed to data analysis, interpretation and draft of the manuscript; all the authors did critical revisions of the manuscript and approved the final manuscript.

Competing interest

The authors declare no conflict of interest.

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Ethical approval

Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

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A large, cross-sectional observational study of serum BDNF, cognitive function, and mild cognitive impairment in the elderly

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Objective: The clinical relationship between brain-derived neurotrophic factor (BDNF) and cognitive function or mild cognitive impairment (MCI) is not well-understood. The purpose of this study was to identify the relationship between serum BDNF and cognitive function and MCI, and determine whether serum BDNF level might be a useful biomarker for assessing risk for MCI in older people.

Materials and Methods: A total of 4463 individuals aged 65 years or older (mean age 72 years) participating in the study. We measured performance in a battery of neuropsychological and cognitive function tests; serum BDNF concentration.

Results: Eight hundred twenty-seven participants (18.8%) had MCI. After adjustment for sex, age, education level, diabetes, and current smoking, serum BDNF was associated with poorer performance in the story memory, and digit symbol substitution task scores. Serum BDNF was marginally associated with the presence of MCI (odds ratio, 95% confidence interval: 1.41, 1.00–1.99) when BDNF was 1.5 SD lower than the mean value standardized for sex and age, education level, diabetes, and current smoking.

Conclusion: Low serum BDNF was associated with lower cognitive test scores and MCI. Future prospective studies should establish the discriminative value of serum BDNF for the risk of MCI.

Keywords: brain-derived neurotrophic factor, cognition, biomarker, dementia, aged

INTRODUCTION

Mild cognitive impairment (MCI) is a transitional condition between normal cognitive function and a clinical diagnosis of probable Alzheimer's disease (AD). MCI, including amnestic MCI, is a pathologically heterogeneous disorder in which many persons exhibiting mixed pathologies (Schneider et al., 2009). Few studies have investigated biomarkers for MCI. Most work has focused on tau and/or Aβ-42 and their association with neuroimaging results and clinical symptoms in persons at risk for AD. Biomarkers for AD and MCI must be established and validated in larger cohorts, and efforts should be made to investigate markers of other aspects of tau and Aβ pathology, including inflammation and trophic factors (Winblad et al., 2004). Neuronal hypertrophy might constitute an early cellular response to AD pathology or reflect a compensatory mechanism that prevents cognitive impairment despite substantial AD lesions (Riudavets et al., 2007; Iacono et al., 2008, 2009). Neuronal cell growth is modulated by factors such as brain-derived neurotrophic factor (BDNF) (Schindowski et al., 2008). BDNF is highly concentrated in the hippocampus (Phillips et al., 1990), important in synaptic plasticity (Kang and Schuman, 1995; Figurov et al., 1996), and contributes to neurogenesis in the dentate gyrus (Takahashi et al., 1999). BDNF plays a pivotal role in age-related memory impairments and is associated with age-related atrophy of the hippocampus. Previous studies have reported that serum BDNF levels are reduced in AD (Gezen-Ak et al., 2013), MCI (Peng et al., 2005; Yu et al., 2008), major depression disorder, and depressive symptoms (Karege et al., 2002; Shimizu et al., 2003; Cunha et al., 2006; Terracciano et al., 2011). A study of neuronal cell cultures found that amyloid peptide at sub-lethal concentrations interfered with neuronal plasticity mediated by BDNF signaling cascade (Tong et al., 2004; Wang et al., 2006). Neuronally differentiated P19 mouse embryonic carcinoma cells stimulated by BDNF showed a rapid decrease in tau phosphorylation (Elliott et al., 2005). However, clinical studies that report lower serum BDNF levels are difficult to interpret because of limited knowledge of potential confounders and mixed results based on patient's age and sex (Bus et al., 2012). Therefore, there is no normal distribution in serum BDNF level, and this may lead to misinterpretation of BDNF levels in studies that used parametric testing with small sample sizes (Ziegenhorn et al., 2007). To establish a cut-off value for serum BDNF is important for clinical purposes, e.g., for helping to increase diagnostic sensitivity. The purpose of this study was to examine the relationships between serum BDNF level and MCI and evaluate whether serum BDNF

level may be useful for assessing MCI risk in older adults using a large sample cohort. We explored the relationship between serum BDNF level and MCI, and various measures of cognitive function in elderly adults.

MATERIALS AND METHODS

STUDY POPULATION

Our study assessed 5104 individuals who were enrolled in the Obu study of health promotion for the elderly (OSHPE). Each individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. To be included in this study, 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 missing BDNF data and characteristics, diagnosed neurological disorders included stroke, Parkinson's disease, AD, and depression, certified long-term care insurance, or functional decline of activities of daily living (ADL). **Figure 1** shows the flow of participants (**Figure 1**). Six hundred forty-one of the 5104 participants were excluded and 4463 older adults (range 65–97 years) were included in this study. The data of 4463 individuals were used to analyze in the present 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.

BDNF MEASUREMENT

Whole blood samples were collected from each patient by venipuncture. To obtain serum, whole blood samples were allowed to coagulate at room temperature (RT) for 30 min and then centrifuged at RT 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 (ELISA) using the DuoSet ELISA Development Kit from R&D Systems (Minneapolis, MN, USA). Assays were performed using a specific human BDNF antibody (Minneapolis, MN, USA); no significant cross reactivity or interference was observed in this assay. Serum samples were diluted 1:50. Sample BDNF concentrations were then determined by non-linear regression from the standard curves. Measurements were performed in duplicate and averaged to give a value in picogram per milliliter, which was then expressed in nanogram per milliliter 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, USA), giving nominal concentrations of 2 and 20 ng/ml, respectively. The assays were performed by one laboratory (SRL Inc., Tokyo, Japan). The repeatability of the BDNF ELISA, as measured by intra-assay precision was 3.8%, and the reproducibility, as measured by inter-assay precision, was 7.6%.

MCI CRITERIA AND COGNITIVE FUNCTION TESTS

We defined MCI based on previous studies (Hanninen et al., 2002; Jungwirth et al., 2005; Yaffe et al., 2011), using the following criteria: (1) subjective memory complaints; (2) objective cognitive impairment [indicated by an age-adjusted score at least 1.5 SD below the reference threshold of any of the tests, all of which are commonly used for detailed neuropsychological assessments] but no general cognitive impairment; (3) no evidence of functional dependency (no need for supervision or external help in performing daily activities); and (4) exclusion from the clinical criteria for dementia. Screening for MCI included a standardized personal interview for collecting sociodemographic and

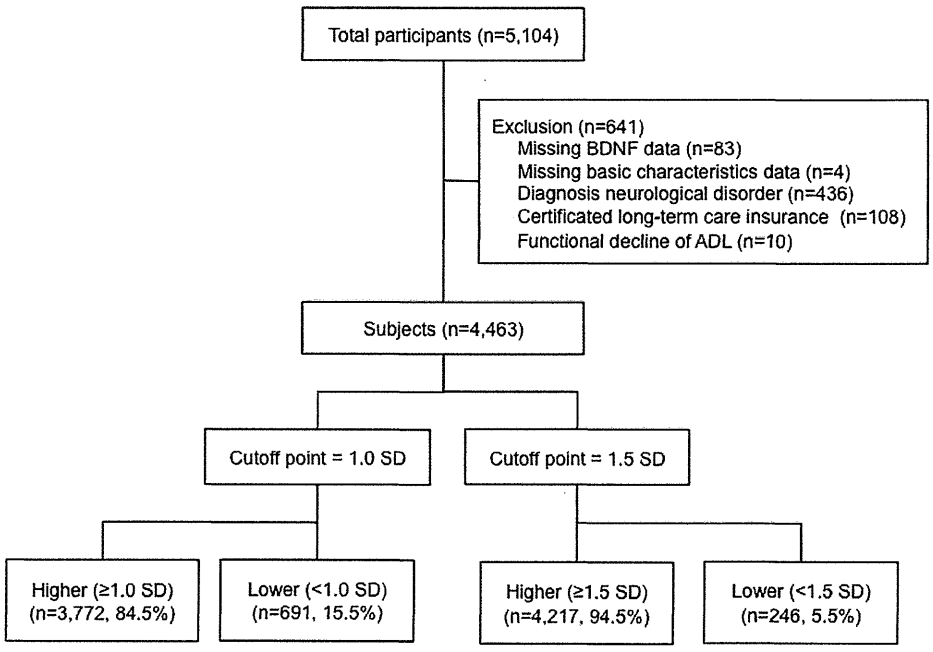

FIGURE 1 | Flow of participants. A total of 4463 participants >65 years of age were included in the study. BDNF levels were measured and the participants were divided into those with higher or lower BDNF levels below 1.0 and 1.5 standard deviations from the mean age- and sex-adjusted BDNF value.

lifestyle data, medical history, and functional status (ADL) data, along with cognitive function testing using the mini-mental state examination (MMSE) (Folstein et al., 1975) and the National Center For Geriatrics And Gerontology-Functional Assessment Tool (NCGG-FAT) (Makizako et al., 2012). Individuals who scored ≤23 points on the MMSE were considered to have general cognitive impairment (Anthony et al., 1982). The NCGG-FAT consists of multidimensional cognitive tasks used to assess word-list memory (delayed recall), story memory (delayed recognition), attention and executive function (tablet version of the Trail Making Test – Part A and B), processing speed (tablet version of the symbol digit substitution test), and visuospatial skill (figure selection). The participants were given 20–30 min to complete the battery of tests and their associated tasks. High test–retest reliability and moderate-to-high validity were previously confirmed in community-dwelling older adults for all components of the NCGG-FAT (Makizako et al., 2012). All tests used in this study had previously established standardized thresholds for the definition of cognitive impairment in the corresponding domain (score <1.5 SD below the age-specific mean) for a population-based OSHPE cohort of healthy older adults.

POTENTIAL CORRELATES

Based on the review articles by Bus et al. (2011, 2012), Ziegenhorn et al. (2007), Knaepen et al. (2010), and Plassman (2010), we selected three demographic variables, one physiological variable, two health status indicators, and three behavioral variables as possible confounding factors of the association between BDNF and cognitive decline (Ziegenhorn et al., 2007; Knaepen et al., 2010; Bus et al., 2011, 2012). The three demographic variables – sex, age, and educational level – were selected as possible confounding factors in determining the association of serum BDNF and MCI. Walking speed – the physiological variable – 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 walkway, with a 2-m section to traverse 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. Histories of heart disease and diabetes were obtained as health status indicators. Behavioral factors, including current smoking, regular exercise, and frequency of going outdoors, were identified during the interview. Participants were asked whether they currently smoked or exercised regularly: responses were either "yes" or "no." Participants were asked how often they traveled to places outside their town during a week.

STATISTICAL ANALYSIS

Student's *t*-test was used to compare BDNF concentrations between men and women. Differences in serum BDNF concentrations were analyzed among four age-groups (65–69, 70–74, 75–79, 80–84, and ≥85 years) by one-way analysis of variance (ANOVA) in both sexes. A linear regression was used to analyze the relationships between BDNF concentration and age and education in both sexes. Participants were divided into two groups according to 1.0 or 1.5 SD from age- and sex-specific mean values among the four age-groups (**Figure 1**). Independent sample *t*-tests or Chi-square tests were used to compare the potential correlates and cognitive performance between: (a) participants who had BDNF levels below 1.0 SD and above 1.0 SD; and (b) participants who had BDNF levels below 1.5 SD and above 1.5 SD. Linear regression analyses (forced-entry) were used to reveal the relationships between BDNF concentration and cognitive performance. Multivariate logistic regression analyses, forced-entry, were used to determine adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs), and to assess independent associations between the serum BDNF levels and MCI. The covariates of sex, age, and educational level, and significant variables in univariate analyses were added to the regression models to evaluate independent associations between BDNF and cognitive performances or MCI. Logistic regression models determined the crude OR and the adjusted OR of BDNF for 1.0 and 1.5 SD. Sensitivity, specificity, and positive and negative likelihood ratios of the BDNF values with MCI were calculated. We excluded the participants who scored ≤23 points on the MMSE and did not complain of memory loss. We used the data of MCI ($n = 827$) and cognitive healthy ($n = 2533$) elderly adults in the logistic regression analyses. 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).

RESULTS

The mean BDNF concentrations were statistically significantly different in men (20.8 ± 5.6 ng/ml) and women (21.2 ± 5.2 ng/ml; $t = 2.162$, $df = 4394$, $P = 0.031$). BDNF concentrations declined with increasing age in both sexes ($F = 24.822$, $df = 3$, $P < 0.001$) (**Table 1**; **Figure 2**). Linear regression found that serum BDNF was

Table 1 | Serum BDNF levels among the four age-groups.

	Men		Women	
	BDNF values 1.0 SD lower than the mean	BDNF values 1.5 SD lower than the mean	BDNF values 1.0 SD lower than the mean	BDNF values 1.5 SD lower than the mean
65–69 years	16.08	13.34	16.75	14.15
70–74 years	15.20	12.52	15.85	13.16
75–79 years	14.82	11.84	15.12	12.57
80 years and over	13.30	10.27	15.05	12.63

associated with age in men ($\beta = -0.123$, $t = -5.750$, $P < 0.001$) and women ($\beta = -0.154$, $t = -7.475$, $P < 0.001$). Education level was associated with serum BDNF in women ($\beta = 0.045$, $t = 2.149$, $P = 0.032$), but not in men ($\beta = 0.012$, $t = 0.564$, $P = 0.573$).

The comparison between participants who had BDNF levels below 1.0 SD and above 1.0 SD, revealed that the participants below 1.0 SD had a higher prevalence of diabetes, a lower proportion of smokers, higher scores of story memory, and a symbol digit substitution task, compared with participants who had BDNF levels above 1.0 SD. The results were similar for the comparison between the participants who had BDNF levels below 1.5 SD and above 1.5 SD. A comparison of MCI prevalence found no significant difference between the participants who had serum BDNF below and above 1.0 SD. In contrast, when serum BDNF was dichotomized according to 1.5 SD below the mean, a significant difference was found in MCI (**Table 2**). The mean BDNF concentrations did not show significant differences between MCI participants (20.9 ± 5.3 ng/ml) and non-MCI participants (21.2 ± 5.4 ng/ml; $t = 1.362$, $df = 3358$, $P = 0.173$).

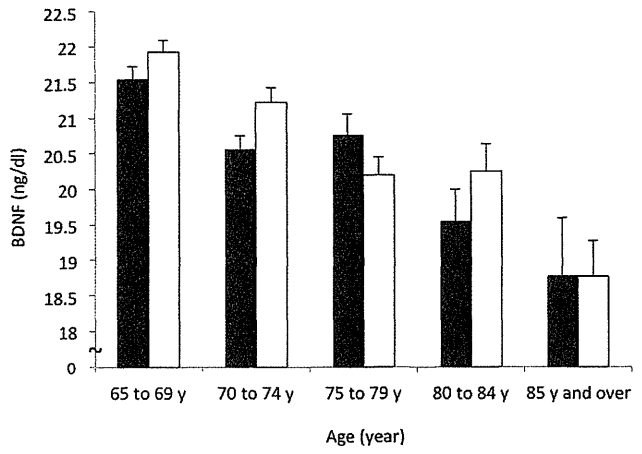

FIGURE 2 | Sex and age differences in serum BDNF concentration. Mean and standard error of serum BDNF levels are shown for each 5-year increment in age. Serum BDNF decreased with aging in men (black bars) and women (white bars; $P < 0.001$) and women showed higher BDNF levels than men ($P = 0.031$).

Table 3 shows the association between serum BDNF and performance on various cognitive function tests using multiple linear regression, adjusted for sex, age, education level, diabetes, and current smoking status. Serum BDNF levels were associated with a decline in story memory ($\beta = 0.027$, $t = 1.958$, $P < 0.05$) and digit symbol substitution test scores ($\beta = 0.027$, $t = 2.172$, $P < 0.05$). There was no significance between BDNF and MMSE for word-list memory, the tablet version of the Trail Making Test – Part A and B, or figure selection.

In all, 827 participants (18.8%) had MCI. A total of 691 participants (15.5%) had BDNF levels below 1.0 SD from the mean, and 246 participants (5.5%) had levels below 1.5 SD from the mean. **Table 4** shows the association between serum BDNF levels and the diagnosis of MCI using multiple logistic regression, adjusted for sex, age, education level, diabetes, and current smoking status. The crude logistic model showed significant relationships between MCI and BDNF: 1.5 SD (OR, 1.40; 95% CI, 1.00–1.96),

Table 2 | Comparisons between BDNF levels of 1.0 and 1.5 SD from the mean.

	BDNF levels of 1.0 SD from the mean			BDNF levels of 1.5 SD from the mean		
	Participants above 1.0 SD	Participants below 1.0 SD	*P*	Participants above 1.0 SD	Participants below 1.0 SD	*P*
Sex, women, *n*, %	1919, 50.9	372, 53.8	0.152	2175, 51.6	116, 47.2	0.177
Age, years	71.9 ± 5.4	72.1 ± 5.5	0.395	71.9 ± 5.5	71.8 ± 5.2	0.744
Education level, years, 10[a]	11.4 ± 2.5	11.3 ± 2.5	0.294	11.4 ± 2.5	11.2 ± 2.5	0.237
Walking speed, m/s, 6[a]	1.3 ± 0.2	1.3 ± 0.2	0.236	1.3 ± 0.2	1.3 ± 0.2	0.722
Heart disease, yes, *n*, 2[a]	585, 15.5	124, 17.9	0.109	671, 15.9	38, 15.4	0.844
Diabetes, yes, *n*	474, 12.6	111, 16.1	0.012	538, 12.8	47, 19.1	0.004
Current smoking, yes, *n*, %, 1[a]	392, 10.4	51, 7.4	0.015	430, 10.2	13, 5.3	0.012
Habitual exercise, yes, *n*, 5[a]	2816, 74.8	519, 75.1	0.844	3152, 74.8	183, 74.4	0.876
Going outdoors, times/week, 1[a]	5.9 ± 1.6	5.8 ± 1.7	0.125	5.9 ± 1.7	5.8 ± 1.7	0.841
MMSE score, 6[a]	26.3 ± 2.7	26.2 ± 2.8	0.64	26.3 ± 2.7	26.0 ± 2.8	0.09
Word-list memory score, 19[a]	3.8 ± 2.0	3.8 ± 2.0	0.872	3.8 ± 2.0	3.7 ± 2.0	0.466
Story memory score, 26[a]	6.8 ± 1.9	6.6 ± 1.9	0.029	6.7 ± 1.9	6.4 ± 1.9	0.011
Trail making test – part A, s, 11[a]	21.2 ± 6.9	21.5 ± 7.3	0.261	21.2 ± 7.0	22.0 ± 7.1	0.083
Trail making test – part B, s, 15[a]	43.1 ± 17.9	44.1 ± 18.4	0.173	43.2 ± 17.9	45.3 ± 18.7	0.068
Symbol digit substitution task, 14[a]	38.4 ± 8.4	37.5 ± 8.5	0.013	38.3 ± 8.4	37.2 ± 8.4	0.049
Visuospatial skill score, 85[a]	5.2 ± 1.5	5.2 ± 1.5	0.928	5.2 ± 1.5	5.2 ± 1.4	0.798
Mild cognitive impairment, yes, *n*, %, 73[a]	689, 24.2	138, 24.6	0.244	774, 24.3	53, 31.0	0.047

[a] *Number of missing data.*

Table 3 | Multiple linier regression analyses with serum BDNF, potential confounders, and cognitive tests.

Independent variable	Dependent variables													
	MMSE		Word-list memory		Story memory		Trail making test – part A		Trail making test – part B		Symbol digit substitution task		Visuospatial skill	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
BDNF, ng/ml	0.011	0.442	0.017	0.229	0.027	0.050	−0.008	0.584	−0.022	0.091	0.027	0.030	−0.011	0.472
Sex, men = 1, women = 2	0.156	<0.001	0.160	<0.001	0.107	<0.001	−0.032	0.027	−0.027	0.050	−0.028	0.030	−0.074	<0.001
Age, years	−0.208	<0.001	−0.316	<0.001	−0.322	<0.001	0.354	<0.001	0.400	<0.001	−0.473	<0.001	−0.167	<0.001
Education, years	0.219	<0.001	0.176	<0.001	0.242	<0.001	−0.167	<0.001	−0.235	<0.001	0.230	<0.001	0.192	<0.001
Diabetes, no = 1, yes = 2	0.009	0.512	−0.016	0.253	−0.015	0.254	0.023	0.091	0.006	0.616	−0.036	0.003	−0.015	0.306
Current smoking, no = 1, yes = 2	−0.042	0.004	−0.009	0.522	0.004	0.781	0.031	0.029	0.057	<0.001	−0.059	<0.001	0.012	0.421

Table 4 | Relationships between MCI and BDNF or selected correlates.

	Crude OR		Adjusted OR in BDNF 1.0 SD		Adjusted OR in BDNF 1.5 SD	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
BDNF 1.0 SD, below/above	1.14 (0.92–1.40)	0.244	1.14 (0.92–1.42)	0.236		
BDNF 1.5 SD, below/above	1.40 (1.00–1.96)	0.048			1.41 (1.00–1.98)	0.050
Sex, women/men	1.00 (0.86–1.17)	0.971	0.85 (0.71–1.00)	0.051	0.85 (0.72–1.01)	0.063
Age, years	1.02 (1.01–1.04)	0.003	1.00 (0.99–1.02)	0.977	1.00 (0.99–1.02)	0.942
Education, years	0.82 (0.79–0.85)	<0.001	0.82 (0.79–0.85)	<0.001	0.82 (0.79–0.85)	<0.001
Diabetes, yes/no	1.11 (0.88–1.39)	0.377	1.04 (0.82–1.31)	0.752	1.03 (0.82–1.31)	0.778
Current smoking, yes/no	1.09 (0.84–1.43)	0.517	1.19 (0.90–1.59)	0.23	1.20 (0.90–1.60)	0.208

age (OR, 1.02; 95% CI, 1.01–1.04), and education (OR, 0.82; 95% CI, 0.79–0.85). The adjusted logistic model for BDNF 1.0 SD showed no significant relationship between serum BDNF and MCI. In contrast, when serum BDNF was dichotomized according to 1.5 SD below the mean, a significant association with MCI was found (OR, 1.41; 95% CI, 1.00–1.98). Education was also associated with MCI (OR, 0.82; 95% CI, 0.79–0.85). Sensitivity and specificity of the BDNF values for 1.5 SD were 6.4% (95% CI: 4.8–8.3%) and 95.3% (95% CI: 94.5–96.1%), respectively. Positive and negative likelihood ratios of the BDNF values of 1.5 SD were 1.38 (95% CI: 1.00–1.88) and 0.98 (0.96–1.00), respectively.

DISCUSSION

In our cross-sectional observational study of 4463 community-living older adults, serum BDNF was associated with a decline in story memory and digit symbol substitution test scores, even when adjusted for sex, age, education, diabetes, and current smoking. Moreover, serum BDNF levels of 1.5 SD lower than the age- and sex-adjusted means were associated with a significant risk of MCI. These results suggest that serum BDNF may be a useful biomarker of cognitive function and MCI status in the elderly.

In demographic variables, serum BDNF was higher in women than men. Similar results were found by Trajkovska et al. (2007) using both serum and whole blood BDNF, whereas they were in contrast to other studies using only serum BDNF (Lang et al., 2004; Ziegenhorn et al., 2007). Another study found a significant interaction of age and menopausal state with BDNF in women, with age-related increases serum BDNF premenopause and age-related decreases postmenopause (Bus et al., 2011). Estrogen levels are significantly associated with BDNF levels (Scharfman and MacLusky, 2006), so the postmenopausal drop in estrogen could result in decreased serum BDNF. Therefore, the differences in serum BDNF levels in men and women might be related to sex hormone differences. However, it is difficult to draw conclusions with cross-sectional approaches, and longitudinal studies are needed.

Among lifestyle measures, diabetes and current smoking showed significant differences between the participants who had high and low serum BDNF levels. Low levels of BDNF accompanied impaired glucose metabolism. Krabbe et al. reported