be accounted for when defining sarcopenia.[31] In the current study, TUG was a significant predictor of the onset of both sarcopenia and severe sarcopenia, suggesting that declines in balance may play a role in the development of sarcopenia.

The results revealed that age, BMI, and calf circumference were predictive of declines in all components of sarcopenia (ie, SMI, grip strength, and walking speed). HDL, cystatin C, and knee pain were all positively associated with the risk for decline in walking speed. Heart disease and hyperlipidemia were predictors of SMI decline, and regular exercise habit was protective against grip strength decline. These novel findings illustrate the predictors of the components of sarcopenia. The predictors were different for each component, and thus should be analyzed separately, as each is a complex condition itself.

The analyses also showed protective effects of higher albumin levels for declines in SMI and walking speed, as well as the development of presarcopenia. Previous studies suggested that low serum albumin is associated with weaker muscle strength in older people,[32] and even further that the increased risk of disability with low serum albumin concentrations may reflect an association with sarcopenia.[33] Therefore, because low albumin is associated with low nutritional status, muscle strength and/or mass may decline due to degradation of protein synthesis caused by malnutrition.[32]

There are several limitations that should be taken into account. First, investigation into the mechanism of the relationships observed was beyond the scope of this study. Although interesting associations were found, we could not determine causality or the mechanisms behind such relationships. Second, this study focused only on the incidence and predictors of sarcopenia in elderly women, and not in men. Therefore the conclusions made cannot be generalized to the population as a whole. However, sarcopenia is a greater public health problem in women than men because women live longer and have higher rates of disability.[34] Further population-based studies are necessary to identify the predictors of sarcopenia.

Based on the results of this study, the predictors of severe sarcopenia included age, BMI, BMD, calf circumference, TUG, and cystatin C. The novelty of the study lies in the relationship between cystatin C and severe sarcopenia. Kidney dysfunction before the development of sarcopenia may indicate a fivefold increase in the odds of sarcopenia onset, based on our longitudinal data. Further research is needed to confirm these results in larger populations.

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Appendix 1

Comparison of Selected Baseline Variables Between Participants of the On-site Survey (Followed) and Dropouts

Variables	Followed (n = 575)	Postal Survey (n = 554)	Institutionalized (n = 38)	Died (n = 39)	No contact (n = 83)	*P* Value*	Post Hoc†
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	78.01 ± 2.5	78.7 ± 2.7	78.4 ± 3.0	79.7 ± 2.8	79.2 ± 2.6	<.001	F<Pst, D, N
Height (cm)	148.4 ± 5.3	147.6 ± 5.6	148.0 ± 6.8	147.2 ± 6.0	146.8 ± 5.5	.027	
Body weight (kg)	50.2 ± 7.9	49.7 ± 7.9	48.6 ± 9.0	49.5 ± 8.1	48.4 ± 8.2	.272	
BMI (kg/m^2)	22.8 ± 3.3	22.8 ± 3.2	22.2 ± 3.9	22.8 ± 3.2	22.5 ± 3.7	.782	
BMD (g/cm^2)	0.29 ± 0.1	0.29 ± 0.06	0.27 ± 0.06	0.28 ± 0.06	0.28 ± 0.06	.104	
Muscle mass (kg)	31.0 ± 3.5	30.6 ± 3.7	30.0 ± 3.8	31.1 ± 4.4	30.2 ± 3.7	.148	
Appendicular muscle mass (kg)	15.5 ± 1.9	15.3 ± 2.0	14.9 ± 1.9	15.6 ± 2.5	15.2 ± 2.1	.189	
Calf circumference (cm)	33.4 ± 2.9	33.0 ± 2.9	32.6 ± 3.3	33.4 ± 3.8	32.6 ± 3.1	.071	
Grip strength (kg)	18.9 ± 4.1	18.0 ± 4.0	18.0 ± 4.0	17.0 ± 3.8	17.4 ± 3.9	<.001	F>Pst, N
Knee extension strength (Nm)	59.9 ± 16.5	56.8 ± 14.6	52.7 ± 14.1	53.4 ± 14.9	52.7 ± 14.6	<.001	F>Pst, N
Usual walking speed (m/s)	1.3 ± 0.2	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	<.001	F>Pst, I, D, N
Timed up & go (s)	7.4 ± 2.8	8.3 ± 3.6	9.3 ± 5.2	9.5 ± 6.3	9.3 ± 4.0	<.001	F<Pst, I, D, N
Creatinine (mg/dL)	0.65 ± 0.15	0.67 ± 0.18	0.63 ± 0.12	0.72 ± 0.23	0.67 ± 0.17	.020	
Albumin (g/dL)	4.28 ± 0.2	4.27 ± 0.24	4.27 ± 0.23	4.22 ± 0.30	4.27 ± 0.26	.692	
25 Hydroxyvitamin D (ng/ml)	22.16 ± 6.4	21.64 ± 6.34	20.21 ± 6.89	23.11 ± 11.91	21.55 ± 7.68	.236	
β 2-microglobulin (mg/L)	1.91 ± 0.5	2.02 ± 0.63	2.05 ± 0.70	2.36 ± 0.98	2.10 ± 0.66	<.001	D>Pst>F
Cystatin C (mg/L)	0.93 ± 0.2	0.97 ± 0.23	0.96 ± 0.25	1.11 ± 0.36	0.99 ± 0.27	<.001	D>Pst>F
Chronic conditions and lifestyle variables							
Falls (yes, %)	16.2	19.2	18.4	23.1	31.3	.020	
Multiple falls (yes, %)	3.7	4.2	7.9	5.1	13.3	.003	
Pain (yes, %)	60.7	66.7	71.1	64.1	62.7	.252	
Knee pain (yes, %)	32.2	33.4	43.2	26.5	31.2	.607	
IADL (disability, %)	3.0	6.0	10.5	7.7	8.4	.023	
Regular exercise (yes, %)	40.7	25.1	23.7	28.2	20.5	<.001	
Knee osteoarthritis history (yes, %)	23.9	22.4	13.2	20.5	26.5	.532	
Osteoporosis history (yes, %)	28.2	34.3	34.2	30.8	32.5	.274	
Heart disease history (yes, %)	19.3	20.2	13.2	35.9	21.7	.110	
Hyperlipidemia history (yes, %)	39.8	38.3	28.9	33.3	37.8	.670	

BMI, body mass index; BMD, bone mineral density; IADL, instrumental activities of daily living; F, followed; Pst, postal survey; I, institutionalized, D, died, N, no contact.

*One-way analysis of variance for continuous variables and chi-square test for categorical variables.

†A post hoc analysis was performed using the Scheffe method.

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Serum brain-derived neurotrophic factor level in elderly women depression: A community-based study

Masahiro Hashizume [c,*], Mitsugu Hachisu [a], Hideyo Yoshida [b], Miji Kim [b], Hun Kyung Kim [b], Yuichi Amano [a], Chie Hasegawa [c], Takao Suzuki [d], Kazushige Ihara [e]

[a] Division of Clinical Pharmacy, Department of Pharmacotherapeutics, School of Pharmacy, Showa University, Japan
[b] Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Japan
[c] Department of Psychiatry, Faculty of Medicine, Dokkyo Medical University, Japan
[d] National Institute for Longevity Sciences, Japan
[e] Division of Public Health, Department of Social Medicine, Faculty of Medicine, Toho University, Japan

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ABSTRACT

Objectives: Serum levels of brain-derived neurotrophic factor (BDNF) have been shown to be lower in patients with major depressive disorder (MDD) than in healthy persons. Although several studies have examined the associations between serum BDNF levels and broader categories of depression identified by psychiatrists or depressive symptoms measured with depression scales among nonpatient populations, some of these studies did not consider possible confounders and included mostly young or middle-aged subjects and nonrepresentative control subjects, such as volunteers and patients' relatives. Therefore, it remains unclear that whether MDD, broader categories of depression, or depressive symptoms in the elderly are associated with BDNF. The present study examined these associations in a community sample and controlled for confounders.
Methods: The subjects were 538 women aged 78 to 88 years who had participated in a follow-up survey of a cohort and had scored 24 or more on the Mini-Mental State Examination. Two depression scales were administered, and, using the Structured Clinical Interview for DSM-IV, psychiatrists identified 53 persons having any mood disorder (AMD) — 8 with MDD and 45 with other types of depression according to the DSM-IV or its research criteria — and 106 healthy controls.
Results: Subjects with MDD had serum BDNF levels lower than did controls but subjects with AMD did not. The severity of depressive symptoms assessed with either of the 2 depression scales was negatively correlated with serum BDNF levels in all subjects and in subjects remaining after persons with MDD or AMD were excluded. These associations were significant after controlling for possible confounders.
Conclusion: We have found an association between MDD and serum BDNF levels in old–old women, as has previously been found in younger patients. Although serum BDNF levels were not found to be associated with the broader category of depression, they were associated with depressive symptoms among subjects without clinical depression.

1. Introduction

Depression is a prevalent psychiatric disorder in the elderly and a risk factor for both functional decline (Bruce et al., 1994a; Penninx et al., 2000; Penninx et al., 1999a) and early death (Bruce et al., 1994b; Penninx et al., 1999b). Early detection of depression allows appropriate treatment and mitigation of its effects, although elderly persons with depression are less likely than younger persons to receive treatment (Charney et al., 2003; Kessler et al., 2010). This difference might be partly attributed to the difficulty of diagnosing depression in the elderly which, in turn, might be due to differences in the phenomenology of depression between older and younger persons (Brodaty et al., 2005; Brown et al., 1984; Gallagher et al., 2010; Hybels et al., 2012). Organic pathology in the brain is often assumed to be an underlying cause of the phenomenological differences of depression in the elderly. To understand the organic pathology of the brain, many studies on the basis of the vascular depression hypothesis (Alexopoulos et al., 1997) have been conducted being driven with development of imaging technologies.

In contrast, few studies on the basis of the neurotrophin hypothesis (Duman et al., 1997), which is one of the main hypotheses of depression at the present day, have been conducted in older persons with depression.

Abbreviation: BDNF, brain-derived neurotrophic factor.

* Corresponding author at: Department of Psychosomatic Medicine, Faculty of Medicine, Toho University School of Medicine, 6-11-1 Omorinishi, Ota-ku, Tokyo 143-8541, Japan.
E-mail addresses: 028704hm@med.toho-u.ac.jp, hashi2@med.toho-u.ac.jp (M. Hashizume).

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The utilization of brain-derived neurotrophic factor (BDNF) in the blood in addition to that in postmortem brain has provided much evidence to support the neurotrophin hypothesis of depression showing that serum levels of BDNF are lower in patients with major depressive disorder (MDD) than in healthy control subjects (Karege et al., 2002; Shimizu et al., 2003) and increase after antidepressant treatment (Aydemir et al., 2005; Gervasoni et al., 2005). Although meta-analyses have confirmed the lower serum levels of BDNF in MDD (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Molendijk et al., 2014; Sen et al., 2008), most studies have included only young or middle-aged subjects.

Few studies have examined the association between serum BDNF and depression in the elderly. To the best of our knowledge, only 1 community-based study (Ziegenhorn et al., 2007) and 1 study in a clinical setting (Diniz et al., 2010) have examined the association exclusively in the elderly, whereas other studies have examined the association in both young subjects and older subjects (Bus et al., 2012; Terracciano et al., 2011). The study of Diniz et al. in elderly subjects found that serum levels of BDNF were lower in patients with MDD than in healthy control subjects, as did studies in younger subjects. The community-based study by Ziegenhorn et al., however, found no such association.

Some researchers have tried to take findings about BDNF levels and depression obtained in patient groups and extend them to nonpatient groups, drawn from the general population or community-dwellers (Bhang et al., 2012; Bus et al., 2012; Elfving et al., 2012; Harvey et al., 2013; Terracciano et al., 2011; Ziegenhorn et al., 2007). However, half of the studies in nonpatient populations, comprising mainly young or middle-aged persons, did not show the same association between serum BDNF and depression (Elfving et al., 2012; Harvey et al., 2013; Ziegenhorn et al., 2007). The failure to confirm the results of previous studies seems partly due to depression in population-based or community-based studies tending to be less severe than MDD in clinical studies (Elfving et al., 2012; Ziegenhorn et al., 2007) or to depression in a population-based study being identified with a depression scale (Harvey et al., 2013). These findings might have been confirmed by community-based studies if they had identified MDD according to standard clinical criteria, as clinical studies do.

Population-based or community-based studies using depression scales, however, can examine a continuous association between depression and serum BDNF in samples comprising both healthy persons and depressed persons (Bhang et al., 2012; Bus et al., 2012; Terracciano et al., 2011), and, therefore, these studies have broader public health implications. Furthermore, population-based studies, regardless whether depression is assessed quantitatively or categorically, can use samples that are more representative than those in clinical studies and can more easily control confounders. Some studies have reported confounders for any association between depression and serum BDNF (Bus et al., 2012; Elfving et al., 2012).

In the present study, we examined the continuous associations of serum BDNF levels with depression, measured with depression scales, among older community-dwellers while considering possible confounders. We also examined the association of serum BDNF with either MDD alone or all mood disorders, including MDD, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 2000), in the same samples. We believe that simultaneous examination of the associations in the community sample would reconcile differences in previous findings between younger patients and older patients and between nonpatient studies and clinical studies.

2. Methods

2.1. Study subjects

The subjects were 575 participants of a survey carried out for 9 days in October 2012. The survey was a follow-up of a cohort of 1289 participants of a 2008 baseline survey that targeted all 10,948 women aged 75 to 84 years in an urban area in Tokyo. The subjects underwent physical and psychological assessments, including hematological examination; the Mini-Mental State Examination (MMSE) (Folstein et al., 1975); and assessment with 2 depression scales. Subjects who were suspected to have depression on 1 of the depression scales (the Depression Scale in Basic Checklist [DSBC]) (Fujisawa et al., 2005), and who scored 24 points or higher on the MMSE were asked to undergo a psychiatric evaluation. Among those who were not suspected to have depression on the basis of the DSBC, consecutive participants on 3.5 days of the survey periods were also asked to undergo psychiatric evaluation.

We assert that all procedures contributing to this study comply with the ethical standards of the relevant national committees on human experimentation. Ethical approval was granted by the ethics committee of the Toho University School of Medicine (Registration Number 24034). Informed consent was obtained before the follow-up survey.

2.2. Depression scales

Symptoms of depression were assessed with the Self-Rating Depression Scale (SDS) (Zung, 1967) and the DSBC. The SDS is composed of 20 items that assess the frequency of symptoms on a 4-point scale from 1 (none or a little of the time) to 4 (most or all of the time) during the past several days. This scale yields a total score of 20 to 80, with higher total scores indicating more severe state of depression. The SDS was self-administered by the subjects but was observed by lay personnel to reduce missing values and adverse ratings for negatively worded items. The DSBC is a 5-item, yes/no question scale that was developed to find depression in the elderly. A yes answer means the presence of a symptom during the last 2 weeks and is given 1 point. The total score ranges 0 to 5, and a total score of 2 or more indicates clinical depression. While psychologists administered the DSBC by reading questions, the test was self-rated and indicated the subjects own responses.

2.3. Psychiatric evaluation

The psychiatric evaluation was carried out within 6 weeks after the survey. Psychiatrists assessed subjects using the A and J modules of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2003) and identified mood disorders during the past 1 month and over the subjects' lifetime. The SCID enabled us to identify any mood disorders (AMD) during the survey when blood for BDNF and other hematological examinations was drawn. Besides MDD, AMD in the present study could include a major depressive episode in partial remission, dysthymic disorder and bipolar disorder I and II according to DSM-IV, minor depressive disorder, according to the criteria sets for further study in DSM-IV (American Psychiatric Association, 2000), and depression that meets the criteria for minor depressive disorder except that there had never been a major depressive episode. The Grid-Hamilton Depression scale (HAMD) (Tabuse et al., 2007) was administered for all cases of mood disorders identified with the SCID, and those subjects who scored 6 points or less on the HAMD were ultimately judged as not having MDD or AMD. Subjects with no lifetime or current mood disorder comprised a control group. Subjects who were under any treatment for depression were excluded from the depression group and the control group. Before the psychiatric evaluation, psychologists conducted pre-interviews, which obtained information on prescribed antidepressants, mainly from prescription notebooks that were given by their family physicians or pharmacists in Japan. Psychiatrists also asked whether the subjects were under treatment.

2.4. Serum BDNF

Blood was withdrawn between 9:00 and 11:00 a.m. or between 1:00 and 4:00 p.m. Soon after being drawn, the samples were centrifuged at 3000 rpm and 4 °C for 15 min, and the sera were transferred to a new

set of polypropylene tubes. The serum samples were stored at −80 °C until measurement. Serum BDNF levels were measured from 4 to 5 months after the survey using the Emax Immuno Assay System (Promega Corp., Madison, WI, USA) according to the manufacturers' protocol. That is, 96-well microplates were coated with an anti-BDNF monoclonal antibody and incubated overnight at 4 °C. The plates were incubated in a blocking buffer for 1 h at room temperature. The samples, which were diluted 50 times with assay buffer and BDNF standard, were placed in the microplate, which were incubated for 2 h while being horizontally shaken at room temperature and then washed with Tris-buffered saline with Tween 20 washing buffer. The plates were incubated with an anti-human BDNF polyclonal antibody at room temperature for 2 h and washed with the washing buffer. The plates were then incubated with an anti-immunoglobulin Y antibody conjugated to horseradish peroxidase for 1 h at room temperature and incubated in the peroxidase substrate of a tetramethylbenzidine solution to induce the color reaction. The reaction was stopped with 1N HCl. The absorbance at 450 nm was measured with an Emax automated microplate reader (Promega Corp.). Each measurement was performed in duplicate. The standard curve was linear from 7.8 to 500 pg/mL, and the detection limit was 10 pg/mL.

2.5. Statistical analyses

We used the Kolmogorov–Smirnov test to evaluate whether the concentration of BDNF was normally distributed. The associations of serum BDNF with either MDD or AMD identified by the psychiatrists using the SCID were assessed with Mann–Whitney U test. The associations of serum BDNF level with total scores of either the SDS or the DSBC were examined with Spearman's correlation coefficients. The association of BDNF with depression identified by psychiatrists or depression assessed with the depression scales was examined with multiple variable analyses (generalized linear models) to control for possible confounders. The representativeness of subjects who participated in the psychiatric evaluation was assessed with the Chi-square (χ^2) test for categorical variables and the Mann–Whitney U test for continuous variables. We performed all analyses with the software program SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. General results

Of the 575 participants in the survey, 571 persons had measurable serum levels of BDNF, and 538 of the 571 scored 24 points or higher on the MMSE (Fig. 1). The serum BDNF had a median of 10.5 ng/mL (range: 0.2–27.3), but the levels were not normally distributed ($p = 0.006$). Characteristics of the 538 subjects and their association with serum BDNF levels are shown in Table 1. Two-thirds of the subjects lived with their family, and most of the subjects were nonsmokers. Blood drawing in the morning and the fasting state were associated with higher BDNF levels. In the 533 persons from whom blood was drawn in a nonfasting state (less than 12 h after the last meal), the serum BDNF level did not differ according to the time since the last meal (Spearman's $\rho = 0.021$; $p = 0.625$; not shown in Table 1).

Of the 538 subjects with measurable serum BDNF levels and scores of 24 points or higher on the MMSE, 94 screened positive for depression on the DSBC, and 69 of those persons participated in the psychiatric evaluation. Of the 446 persons who screened negative for depression on the DSBC, 163 consecutive persons were asked to participate in the psychiatric evaluation, and 122 persons did so.

3.2. Representativeness of the participants of psychiatric evaluation

Among the 94 subjects who screened positive for depression on the DSBC, the 69 subjects underwent psychiatric evaluation and the 25 subjects did not show any difference in the distributions or median values of possible confounders (Table 2). Among persons who screened negative for depression, the 122 subjects participated in psychiatric evaluation and the 41 did not differ in the rate of living alone and the median values of the MMSE score. However, the distributions and medians, including living situation and the MMSE, for the 122 participants without depression on the DSBC did not differ from those of the remaining 324 persons without depression on the DSBC who were not examined by psychiatrists. These results are not shown in Table 2.

3.3. Depression identified by psychiatrists and BDNF

Of the 191 participants of the psychiatric evaluation, 8 had MDD, current episode, and 53 had AMD, current episode, including the 8 with MDD and 1 with double depression (dysthymic disorder overlapped with MDD). Psychiatrists also identified 1 person with bipolar II disorder who was excluded from the AMD group for the following analyses. The control group consisted of 106 persons without current or lifetime mood disorders.

Serum BDNF levels were significantly lower in persons with MDD than in the control group ($p = 0.031$, Table 3). Multivariate analyses confirmed that this association was significant after controlling for the effects of possible confounders, time of blood drawing, and fasting state ($p = 0.030$). There was no difference in BDNF levels between the AMD group and the control group. Table 4 shows BDNF levels by type of AMD. An additional analysis revealed higher BDNF levels in persons with AMD other than MDD (11.7 ng/mL [range: 1.3–25.8]) than in persons with MDD (Mann–Whitney U-test, $p = 0.017$).

In addition to the pre-specified univariate analyses, Mann–Whitney U tests, we performed unpaired t-tests as sensitivity analyses. Mean BDNF levels were lower in the MDD group than in the control group (6.3 [S.D. = 2.7] and 11.4 [S.D. = 6.6] respectively; $p < 0.001$) and did not differ between the AMD and control groups (10.6 [S.D. = 6.0] and 11.4 [S.D. = 6.6] respectively, $p = 0.455$).

3.4. Depression assessed by depression scales and BDNF

In the 538 subjects analyzed, the total SDS scores were negatively correlated with serum BDNF levels. The association was statistically significant ($p = 0.001$). The correlation between the SDS and serum BDNF level was significant after excluding from the 538 persons either 8 persons with MDD or 53 persons with AMD ($p = 0.004$ and $p = 0.007$, respectively). The higher total DSBC scores were also associated with lower BDNF levels ($p = 0.006$). The correlation between total DSBC scores and serum BDNF levels was significant after either persons with MDD or persons with AMD were excluded ($p = 0.013$ and $p = 0.012$, respectively). These associations were all significant on multivariate analysis after controlling for the effects of possible confounders of blood drawing and fasting state.

4. Discussion

The present study has found that old–old community-dwelling women with psychiatrist-identified MDD had lower serum BDNF levels than did control subjects, whereas persons with AMD did not. The severity of depression quantitatively assessed with either of 2 different depression scales was negatively correlated with serum BDNF levels among all participants: the more depressed subjects were, the lower were their serum levels of BDNF. These associations were significant after controlling for possible confounders.

By conducting a comprehensive survey, which included psychiatric evaluation, we could obtain comparable samples from a community of

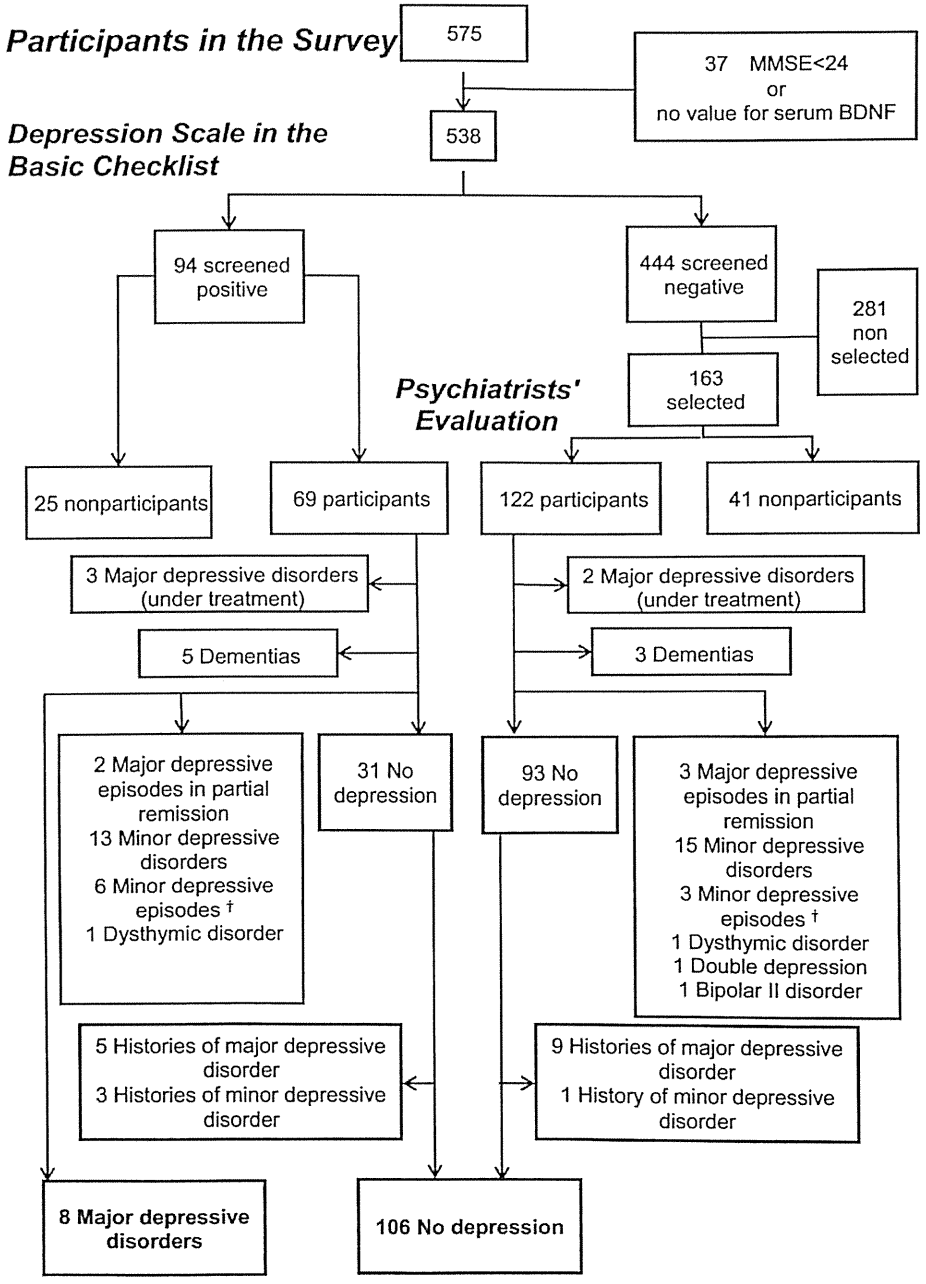

Fig. 1. Flow chart from participants in the survey to diagnostic groups.

depressed persons and healthy persons as controls. This inclusion of both samples is a strength of the present study, as most previous studies used ad-hoc samples, especially for control subjects (Aydemir et al., 2006; Basterzi et al., 2009; Bocchio-Chiavetto et al., 2010; Diniz et al., 2010; Eker et al., 2010; Gervasoni et al., 2005; Gonul et al., 2005; Gorgulu & Caliyurt, 2009; Hu et al., 2010; Huang et al., 2008; Karege et al., 2002, 2005; Karlovic et al., 2013; Matrisciano et al., 2009; Oral et al., 2012; Ozan et al., 2010; Piccinni et al., 2008; Shimizu et al., 2003; Sozeri-Varma et al., 2011; Wolkowitz et al., 2011; Yoshimura et al., 2007). The control subjects in our study seemed to be a representative sample of all subjects without MDD or AMD participating in the survey. Depression identified by psychiatrists was probably representative of the subjects' state. The data we obtained from the comprehensive survey enabled us to consider potential confounders. Recent community-based studies (Bus et al., 2012; Elfving et al., 2012; Harvey et al., 2013) suggested that there are many confounders for any association between BDNF and depression, which was measured with depression scales, whereas most previous studies matched just sex, age, or educational levels between the MDD and control groups (Aydemir et al., 2005, 2006; Basterzi et al., 2009; Diniz et al., 2010; Eker et al., 2010; Gervasoni et al., 2005; Gonul et al., 2005; Gorgulu & Caliyurt, 2009; Karege et al., 2005; Matrisciano et al., 2009; Ozan et al., 2010; Piccinni et al., 2008; Shimizu et al., 2003; Sozeri-Varma et al., 2011; Yoshimura et al., 2007). Therefore, the present study, has considered more confounders to examine the association of BDNF with MDD and AMD identified by psychiatrists as well as depression measured with depression scales.

The present study in elderly persons found a significant association between MDD and BDNF which corresponds to the associations between them found in previous studies, which involved young or middle-aged subjects (Aydemir et al., 2005, 2006; Bocchio-Chiavetto et al., 2010; Gervasoni et al., 2005; Gonul et al., 2005; Gorgulu & Caliyurt,

Table 1
Characteristics and association with serum BDNF levels in the subjects.

		Median (range) or number (%)	ρ value or median (range) of BDNF	p value
Age		82.0 (78–88)	0.063	0.144
Education	Middle school or less	129 (24.0)	10.4 (0.8–26.7)	0.990
	High school or university	409 (76.0)	10.6 (0.2–27.3)	
Household	Living alone	214 (39.8)	10.4 (0.2–27.3)	0.674
	Not living alone	324 (60.2)	10.7 (0.3–27.2)	
Smoking	No	523 (97.2)	10.5 (0.2–27.3)	0.265
	Yes	15 (2.8)	10.8 (3.1–24.4)	
Alcohol	No	421 (78.3)	10.8 (0.2–27.2)	0.280
	Yes	117 (21.7)	10.3 (0.3–27.3)	
Sports activity	2 days or more/week	130 (24.2)	10.6 (0.6–27.3)	0.867
	1 day or less/week	408 (75.8)	10.5 (0.2–27.2)	
BMI		22.5 (12.3–38.5)	0.048	0.266
MMSE		28.0 (24–30)	0.042	0.328
Blood drawing	Morning	234 (43.5)	11.5 (0.2–27.3)	0.043
	Afternoon	304 (56.5)	9.9 (0.2–27.2)	
Fasting state	Non-fasting	533 (99.1)	10.5 (0.2–27.3)	0.019
	Fasting	5 (0.9)	17.1 (12.8–23.7)	

2009; Huang et al., 2008; Karege et al., 2002; Molendijk et al., 2011; Oral et al., 2012). Two recent meta-analyses have reported significantly lower serum BDNF levels in depressed persons than in healthy controls, although studies included in the meta-analyses involved a small number of elderly subjects (Bocchio-Chiavetto et al., 2010; Molendijk et al., 2014). To the best of our knowledge, 2 previous studies have examined the association between BDNF and depression in the elderly, although neither of them sufficiently considered confounders (Diniz et al., 2010; Ziegenhorn et al., 2007). The two studies reached different conclusions: Diniz et al. reported a significant association, while Ziegenhorn et al. found no association. The difference in the results between the 2 studies might be attributed to the differences in the definition of depression, the study settings, or sample characteristics. In the study by Diniz et al., subjects were patients and healthy volunteers, and depression was defined as MDD according to DSM-IV. In the study by Ziegenhorn et al., both persons with depression and healthy control subjects were drawn from a community, and depression was defined as "depression according to DSM-III-R". Of the persons with depression so defined, more than half were not otherwise specified in mood disorder according to the DSM-III-R (American Psychiatric Association, 1987), which is a broader category than MDD according to the DSM-IV. In the study by Ziegenhorn et al. depression was defined similarly as AMD was in the present study. In the present community-based study the result that MDD was associated with lower BDNF levels but that AMD was not suggests that the difference in the definition of depression, not the difference in the study setting, between the 2 previous studies was a likely cause of their differences in their findings regarding the association between BDNF and depression. Together, these findings suggest that older persons with MDD, whether outpatients of a psychiatric department or community-dwellers, have lower serum levels of BDNF than do persons without depression.

In contrast, the present study found that persons with AMD did not have lower serum BDNF than healthy control subjects. As we defined it, AMD was a broad and heterogeneous category of depression which included MDD. However, when persons with MDD were excluded from the AMD group, the remaining subjects had higher BDNF levels than did persons with MDD. Two community-based studies have examined the association between BDNF and some broader categories of depression like AMD, although they included mostly young or middle-aged subjects (Elfving et al., 2012; Harvey et al., 2013). One of these studies found no association (Harvey et al., 2013), and the other found that serum BDNF levels in depressed persons were even higher than those

Table 2
Characteristics of participants and nonparticipants in the psychiatrists' evaluation by screening procedures.

		One point or less on the DSBC			Two points or more on the DSBC		
		Median (range) or number (%)			Median (range) or number (%)		
		Participants n = 122	Nonparticipants n = 41	p value	Participants n = 69	Nonparticipants n = 25	p value
Age		81 (79–88)	82 (78–87)	0.634	82 (79–88)	81 (79–87)	0.509
Education	Middle school or less	28 (23.0)	11 (26.8)	0.673	22 (31.9)	3 (12.0)	0.066
	High school or university	94 (77.0)	30 (73.2)		47 (68.1)	22 (88.0)	
Household	Living alone	51 (41.8)	9 (22.0)	0.025	27 (39.1)	12 (48.0)	0.483
	Not living alone	71 (58.2)	32 (78.0)		42 (60.9)	13 (52.0)	
Smoking	No	117 (95.9)	39 (95.1)	1.000	68 (98.6)	24 (96.0)	0.463
	Yes	5 (4.1)	2 (4.9)		1 (1.4)	1 (4.0)	
Alcohol	No	96 (78.7)	38 (92.7)	0.057	60 (87.0)	19 (76.0)	0.215
	Yes	26 (21.3)	3 (7.3)		9 (13.0)	6 (24.0)	
Sports activity	2 days or more/week	33 (27.0)	9 (22.0)	0.680	14 (20.3)	4 (16.0)	0.772
	1 day or less/week	89 (73.0)	32 (78.0)		55 (79.7)	21 (84.0)	
BDNF		10.9 (0.7–26.4)	11.0 (0.3–25.3)	0.569	9.3 (1.1–24.8)	7.5 (0.4–22.3)	0.114
BMI		22.4 (13.6–38.5)	22.8 (17.0–33.8)	0.105	22.2 (12.3–31.7)	21.6 (15.8–34.6)	0.291
MMSE		28 (24–30)	27 (24–30)	0.017	28 (24–30)	28 (25–30)	0.208
Blood drawing	Morning	61 (50.0)	22 (53.7.0)	0.721	27 (39.1)	13 (52.0)	0.346
	Afternoon	61 (50.0)	19 (46.3)		42 (60.9)	12 (48.0)	
Fasting state	Non-fasting	120 (98.4)	40 (97.6)	1.000	68 (98.6)	25 (100.0)	1.000
	Fasting	2 (1.6)	1 (2.4)		1 (1.4)	0 (0.0)	

Table 3
Characteristics by groups of major depressive disorder (MDD), the control, and any mood disorders (AMD).

		Median (range) or number (%)		p value [a]	Median (range) or number (%)	p value [b]
		MDD n = 8	Control n = 106		AMD n = 53	
Age		82 (79–86)	81 (79–88)	0.973	82 (79–87)	0.845
Education	Middle school or less	4 (50.0)	24 (22.6)	1.000	15 (28.3)	0.441
	High school or university	4 (50.0)	82 (77.4)		38 (71.7)	
Household	Living alone	3 (37.5)	44 (41.5)	1.000	19 (35.8)	0.606
	Not living alone	5 (62.5)	62 (58.5)		34 (64.2)	
Smoking	No	8 (100.0)	100 (94.3)	0.358	53 (100.0)	0.180
	Yes	0 (–)	6 (5.7)		0 (–)	
Alcohol	No	8 (100.0)	83 (78.3)	0.355	44 (83.0)	0.538
	Yes	0 (–)	23 (21.7)		9 (17.0)	
Sports activity	2 days or more/week	2 (25.0)	27 (25.5)	1.000	14 (26.4)	1.000
	1 day or less/week	6 (75.0)	79 (74.5)		39 (73.6)	
BDNF		5.9 (2.7–11.0)	10.9 (0.9–24.8)	0.031	11.0 (1.3–25.8)	0.530
BMI		20.0 (14.9–23.2)	22.5 (13.6–38.5)	0.096	21.4 (12.3–28.5)	0.112
MMSE		27.5 (25–30)	28 (24–30)	0.643	28 (24–30)	0.574
Blood drawing	Morning	2 (25.0)	52 (49.1)	0.277	17 (32.1)	0.044
	Afternoon	6 (75.0)	54 (50.9)		36 (67.9)	
Fasting state	Non-fasting	8 (100.0)	104 (98.1)	1.000	52 (98.1)	1.000
	Fasting	0 (–)	2 (1.9)		1 (1.9)	

[a] Comparison between the MDD and control groups.
[b] Comparison between the AMD and control groups.

in healthy persons (Elfving et al., 2012). The difference in findings among community-based studies, including the present study, might be due in part to differences in the proportion of cases of MDD among the broader categories of depression, because each depression should be a heterogeneous group including MDD, which might have a lower BDNF level than a group of depressed persons excluding those with MDD. However, both the present study and previous studies obtained the inconsistent result that serum BDNF levels were not lower in broader categories of depression than in healthy control subjects.

In the present study the correlations between serum BDNF levels and symptoms of depression were statistically significant. To the best of our knowledge, no previous studies have examined the continuous association between BDNF and depression in the elderly. Two previous studies, which included both young and elderly subjects, examined the correlation between serum BDNF levels and depression (Bus et al., 2012; Terracciano et al., 2011). As these previous studies did not consider the presence of persons with clinically significant depression, such as MDD and AMD, among their subjects, the association they found among groups of healthy persons might reflect low BDNF levels in persons with clinically significant depression. In the present study the correlation between serum BDNF levels and depression was statistically significant after cases of MDD and AMD had been excluded. Even among people without clinically significant depression, symptoms of depression might decrease BDNF concentrations.

A possible limitation of the present study was that psychiatrists evaluated only one-third of the subjects who scored 24 points or more on the MMSE and that some of the remaining two-thirds of subjects, all nonparticipants, likely had MDD or AMD. These possible missed cases might have affected the obtained correlations between serum BDNF levels and symptoms of depression and might make it difficult to assume that the correlations are the same as those in healthy community-dwellers. However, considering the other results of our study, the number of persons with MDD, who would cause BDNF concentrations to be lower, would be a small percentage of all nonparticipants, and the numbers of persons with AMD other than MDD, which would not be small, would cause low serum BDNF concentrations. Therefore, the significance of the correlations we observed would not have been affected if the possible missed cases of AMD and MDD had been excluded from the analyses. On the other hand, the possible missed cases might have affected the categorical association between MDD or AMD and BDNF. However, the serum levels of BDNF among the possible missed cases would not differ much from the obtained values of MDD and AMD, as there was no difference in characteristics between who did and did not undergo psychiatric evaluation. Therefore, the results of the comparison of BDNF between the MDD or AMD group and the healthy control group would not have differed if the possible missed cases had been included in the analyses. In addition to these limitations caused by possible missed cases, other limitations might also exist. For example, the subjects of the present study were old-old women. Different results might have been obtained if the subjects had been male or young-old, because serum BDNF levels might differ by sex and age. Furthermore, the number of MDD cases was small. Therefore, further studies will be necessary.

In conclusion, although the finding of previous studies did not definitively support the notion that MDD in elderly persons is associated with levels of BDNF, as in younger persons, this association was found by the present study in elderly women by examining more representative and comparable samples than examined in previous studies. The broader category of depression, AMD, did not have lower BDNF levels, as some broader categories of depression in previous studies did not. The present study has also shown a continuous association between serum BDNF and symptoms of depression in the elderly, as has been shown in younger subjects in previous studies.

Table 4
Serum BDNF level by subtypes of any mood disorders (AMD).

Diagnostic categories	n	Median	(Range)
Major depressive disorders	8	5.9	(2.7–11.0)
Major depressive episodes in partial remission	5	14.2	(5.5–19.3)
Minor depressive disorders	28	12.0	(1.3–25.8)
Minor depressive episodes[a]	9	7.0	(1.6–13.5)
Dysthymic disorder	2	12.0	(4.0–20.0)
Double depression	1	12.3	–

[a] They met the criteria for minor depressive disorder except for the criterion that there had never been a major depressive episode.

Disclosures

All authors have no competing interests.

Authors' contributions

Dr. Hashizume, Dr. Hachisu, Dr. Yoshida, Dr. Kim HK, Dr. Kim M, Dr. Suzuki and Dr. Ihara designed the study. Dr. Hashizume and Dr. Ihara wrote the first draft of the manuscript. Dr. Hachisu measured serum levels of BDNF. Dr. Amano and Dr. Hasegawa were involved in data collection. All authors read and approved the final manuscript.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Falls and fractures in participants and excluded non-participants of a fall prevention exercise program for elderly women with a history of falls: 1-year follow-up study

Hunkyung Kim,[1] Hideyo Yoshida[1] and Takao Suzuki[2]

[1]Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, and [2]Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan

Aim: To evaluate the effectiveness of a strength and balance enhancing exercise intervention as a means of preventing falls in community-dwelling elderly Japanese women with a history of falls, while comparing functional fitness, fall and fracture rate in excluded subjects.

Methods: A 1-year follow-up trial was carried out on 105 participants over the age of 70 years, who were randomly assigned to the exercise or education group, and also on 91 women excluded based on the exclusion criteria. The exercise group attended a 60-min exercise class twice a week for 3 months. Falls, injuries, fractures, and functional fitness assessments were measured at baseline, post-intervention and 1-year follow up.

Results: During the follow up, fall rates were 19.6% in the exercise group, 40.4% in the education group and 40.8% in excluded subjects ($\chi^2 = 7.069$, $P = 0.029$). Compared with the exercise group, the odds ratio (OR) for falls was greater in the education group (OR 2.78, 95% confidence interval (CI) 1.17–6.96) and excluded participants (OR 2.83, 95%CI 1.25–6.80). The OR for fractures was over fourfold greater in excluded participants (OR 4.30, 95% CI 1.02–9.70) than the exercise group.

Conclusions: The exercise intervention for participants with fall history effectively decreased incidences of falls and fractures. However, fall and fracture rates in excluded people were high. Further research focusing on feasible countermeasures for falls in excluded people who are at high risk of fractures is required. **Geriatr Gerontol Int 2014; 14: 285–292.**

Keywords: exercise program, fall history, falls, fractures, participants and excluded non-participants.

Introduction

Falls and the resulting injuries, such as fractures, as well as fear of falling, activity restriction, and functional decline are among the most serious and common health problems in the elderly.[1,2] Falls in elderly people are not random events, but can be predicted through assessing several risk factors, such as reduced muscle strength and impaired balance.[3] These risk factors can be modified using exercise as either a stand-alone fall prevention intervention or as a component of a multifaceted program. Exercise interventions focusing on balance and muscular strengthening can reduce falls and fall-related factures in those with low bone mineral density.[4] Many studies have sought to establish the specific effects of fall prevention programs;[5–7] however, in these previous trials, many potential participants were excluded based on the author's exclusion criteria.[8–10] One study indicated that such excluded participants were older and in poorer health than the included participants, suggesting that these excluded participants are more likely to be at high risk for falls than those included in the trial.[8] In order to substantially reduce falls in the community-dwelling elderly population as a whole, preventative fall programs should be provided not only for intervention participants, but also for excluded participants. Nevertheless, little is known about the fall-related characteristics of excluded participants, who are at a high risk of falling.

The purposes of the present study were to evaluate the effectiveness of an exercise intervention targeting the enhancement of muscular strength and improvement of balance for fall prevention in independent

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Correspondence: Dr Hunkyung Kim PhD, Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, 35-2 Sakaecho, Itabashi-ku, Tokyo, Japan 173-0015. Email: kimhk@tmig.or.jp

community-dwelling elderly Japanese women with a history of falls, and to examine functional fitness, fall rate and fall-related injury in excluded participants.

Methods

Participants

The baseline survey was carried out in November 2007, on a random sample of 1141 women who were randomly selected from the Basic Resident Register of women aged 70 years and older residing in the Itabashi ward of Tokyo as of 1 April 2007. A total of 196 women (17.2%) who reported fall experience in the previous year were classified as potential participants.

The inclusion criteria were: (i) age ≥70 years; (ii) experienced at least one fall incident in the previous year; and (iii) no missing fall-related baseline data. The exclusion criteria included: (i) severe knee or back pain; (ii) severe walking disability; and (iii) unstable cardiac conditions.[11,12] A total of 91 women (91/196, 46.2%) were excluded based on the exclusion criteria (Fig. 1).

The study protocol was approved by the Clinical Research Ethics Committee of the Tokyo Metropolitan Institute of Gerontology (TMIG). The procedures were fully explained to all participants, as well as all of those who were excluded, and written informed consent was obtained.

Randomization

Out of 196 people who had fall experience, 105 were randomly assigned into either the exercise group ($n = 52$) or the education group ($n = 53$) based on computer generated random numbers, and 91 excluded participants were not included in the randomization. The randomization procedure was blinded, and the investigators evaluating the effects of the exercise treatment were blind to intervention allocations.

Outcome measures and data collection

The primary outcome variables of this trial were the occurrence of falls, repeated falls, injuries and fractures, assessed by face-to-face interviews at baseline and after the intervention, and also by self-reported fall diaries collected at the 1-year follow up.[13] Secondary outcome measures included changes in muscle strength, walking ability and balance.

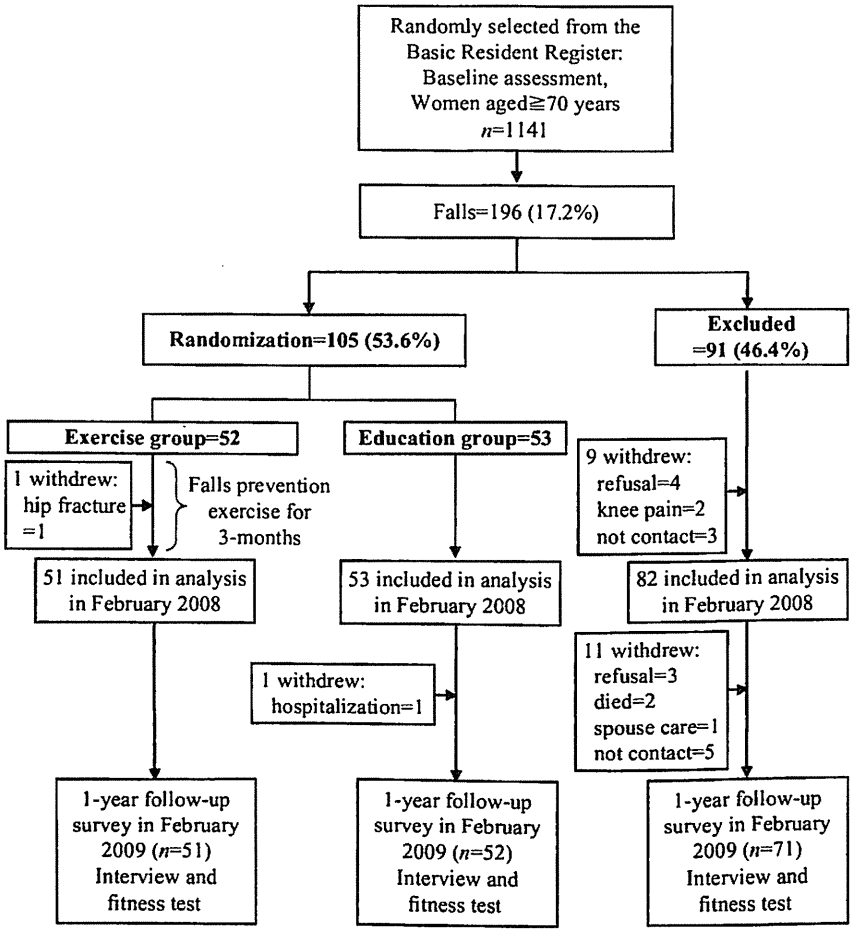

Figure 1 Flow chart showing inclusion, exclusion, randomization and follow-up procedures.

Interview survey

Fall data was collected by face-to-face interviews. At baseline, history of falls was assessed by the question "Have you experienced any falls during the past year?" A person who responded "yes" was defined as a faller, and the number of falls, repeated falls, injurious falls and fractures were evaluated. Repeated falls was assessed as more than two falls in the previous year. A fall was defined as an event that resulted in a person coming to rest inadvertently on the ground or other lower level,[14] and an injurious fall was defined as a fall resulting in physical injury, such as a bruise, wound, twist and/or fracture.

Anthropometric and physical function measurements

Height and bodyweight measurements were converted to body mass index (kg/m^2). Grip strength was measured using a hand-held Smedley type dynamometer. Usual and maximum walking speeds were measured on a flat walking path of 11 m, with markers at the 3 m and 8 m points. A stopwatch was used to measure the time taken to walk 5 m between the markers. To measure one leg standing time with eyes open, participants were asked to stand on their preferred foot, with one foot lifted off the ground, while gazing at a point set at eye level 1 m away until they placed the other foot down. The longer of two trials were recorded. Knee extension strength was measured in the dominant leg, or the leg without pain, with a dynamometer placed at the ankle joint. Muscle strength was measured as the peak force during isometric extension as the participants were asked to extend the knee with maximum leg power, and the higher measurement of two trials was recorded. Ankle dorsiflexion strength was measured on the dominant leg while the participants were seated with their knees bent at right angles (90°) and feet flat on the floor. A strain-gauge type compact force sensor (LPR-A-1KNS1; Kyowa, Tokyo, Japan) was used to measure dorsiflexion strength, where the sensor was placed in contact with the dorsal surface of the foot and strength was measured at its peak force in maximal isometric dorsiflexion. Bone mineral density (BMD) of the distal radius and ulna of the non-dominant forearm was measured by the dual-energy X-ray absorptiometry (DEXA) method using a DTX-200 osteometer (Osteometer MediTech, Signal Hill, CA, USA).[15]

Exercise

The exercise group attended a group-based 60-min exercise class focusing on muscle strength and balance training held at the TMIG health promotion center twice a week for 3 months. Participants who attended 15 or more sessions out of the 24 exercise sessions (60%) were considered to have completed the trial.

Each exercise session consisted of a 5-min warm-up, 30 min of strengthening exercise, 20 min of balance training and 5 min of cool-down. The strengthening exercises were carried out in a progressive sequence from the seated to standing positions. For each type of exercise, participants were instructed to complete up to eight repetitions of the movements. When the exercises were executed without significant fatigue or loss of proper execution, the resistance was increased. Progressive resistance was also provided through the use of resistance bands or ankle-weights. Each individual's ability to increase resistance was assessed by the principal investigator along with the exercise instructor and assistant trainers. The intensity was maintained at approximately 12–14 on the Borg Rate of Perceived Exertion scale.[16]

Chair exercise

Repetitions of ankle dorsiflexions, heel raises, knee extension, leg lifts and more, were carried out seated on the chair, and progressed to standing behind the chair.

Resistance band (Thera-Band) exercise

Seated double-arm pull-backs holding the band horizontally in front of the chest, looped ankle press, looped toe lifts and more.

Ankle-weight exercise

Weights of 0.50 kg, 0.75 kg, 1.00 kg and 1.50 kg were used in accordance with each participant's strength level. The exercises carried out with these ankle-weights included seated knee flexion/extensions, standing knee flexion/extensions, ankle dorsiflexions and others.

Balance training

Standing on one leg, standing on one leg while leaning forward, backward, to the left or right, kneeling on one leg, side stepping on alternate legs, tandem walk, five basic forms of Tai Chi and other items.

Health education

Participants in the education group took a 60-min class held at the TMIG health promotion center once a month for 3 months, a total of three times. The classes focused on undernutrition, cognitive function and oral hygiene, which were taught by research scientists who specialized in each field.

Excluded participants

Excluded participants were asked to continue daily life habits, and were not provided with specific instructions

on fall prevention. The excluded participants were sent reminders, inviting them to attend the surveys that were carried out 3 months after the baseline survey (post-intervention), and after the 1-year follow up.

Follow up and fall diary

During the 1-year follow-up period, the participants in the exercise group attended 1-h exercise classes once a month. All participants were encouraged to carry out two to three sets of each exercise introduced during the group exercise sessions, at least three times a week. To accurately monitor the exercise times and the number of sets carried out during the follow-up period, "Exercise Record Sheets" were distributed to the participants to also document the time and number of exercise sets carried out at home each day. The "Exercise Record Sheets" were collected once a month for the group exercise class, and analyzed to calculate the mean exercise frequency per week and the mean exercise time per day.

Fall diaries were distributed at the post-test survey in the exercise, education and excluded groups, and they were instructed to individually record any fall occurrences during the follow-up period, including the date of any falls, fall-related injuries and the fall environment.[9] The diaries were collected at the final survey after the 1-year follow-up period.

Data analysis

Sample size calculations using univariate repeated measures analysis of variance (ANOVA) to determine significant differences in fall related events at baseline, post-intervention and at 1-year follow up ($\alpha = 0.05$, power = 0.80), with an effect size of 0.15, required a sample size of 52 participants.[17] Means and standard deviations were calculated for each variable, and a one-way ANOVA was used to test differences between the exercise, education and excluded groups. A two-way repeated measures ANOVA was carried out on outcome variables. Significant interactions were examined, using the Schaffer's post-hoc analysis, to determine if effects were greater in the exercise, education or excluded group. A χ^2-test assessed the frequency of pre-, post-intervention and follow-up fall events for each group. Fall rate was calculated as the percentage of fallers. Multiple logistic regressions were carried out to estimate the associations between the groups and falls during the 1-year follow up. *P*-values less than 0.05 were considered significant. All analyses were carried out using SPSS software, Windows version 15.0 (SPSS, Tokyo, Japan).

Results

There were no statistically significant differences in baseline measures between the exercise and education groups. The excluded participants were significantly older, had slower walking speeds and weaker ankle dorsiflexion strength at baseline (Table 1).

Two participants (1.9%) could not complete the trial after the randomization because of hospitalization ($n = 1$) and hip fracture ($n = 1$; Fig. 1). The mean attendance rate was 75.3% (range 64.0–86.0%) during the intervention period and 70.6% during the follow-up period. The mean frequency at which the exercise series was carried out at home during the follow up was 3.4 times per week (23.5% carried out every day, 47.1% 2–3 times per week, 29.4% once or less per week), and the mean exercise time was 24.9 min.

The comparison of pre- to post-intervention measurements showed that the exercise group significantly increased in one leg standing time, knee extension strength and ankle dorsiflexion strength; whereas the education and excluded group showed no significant improvement (Table 2). One leg standing time decreased in the excluded group. Knee extension strength and dorsiflexion strength also declined steadily from pre- to post-intervention, and decreased after the 1-year follow up in both the education and excluded groups. No significant differences were seen in maximum walking speed and grip strength between any of the interventions.

During the 1-year follow-up period, 60 participants experienced falls: 22 repeated falls, 42 injurious falls and 11 fractures. The incidences of falls were 19.6% ($n = 10$) in the exercise group, 40.4% ($n = 21$) in the education group and 40.8% ($n = 29$) in the excluded group ($\chi^2 = 7.069$, $P = 0.029$). There were no significant differences between any of the groups in repeated falls and injurious falls (repeated falls: $P = 0.329$; injurious falls: $P = 0.546$; Table 3). Of the 11 total fractures, one fracture occurred in the exercise group, two fractures in the education group and eight fractures in excluded participants (Fisher's exact test = 0.043).

Analysis of the data obtained on falls, repeated falls, injurious falls and fractures showed that the odds ratio for falls was greater in the education (odds ratio [OR] 2.78, 95% confidence interval [CI] 1.17–6.96) and excluded participants (OR 2.83, 95% CI 1.25–6.80). Fracture incidence was more than fourfold greater in excluded participants (OR 4.30, 95% CI 1.02–9.70) compared with the exercise group (Table 4).

Discussion

The current study is one of the first attempts to collect and analyze functional fitness and fall data not only from the exercise program participants, but also from among the excluded people. Many studies have reported that fall experience is a risk factor for repeated falls;[18,19] therefore, this study focused on elderly women with fall experience, and assessed the effects of exercise on this

Table 1 Selected variables characteristics of participants at baseline by study group

Variables†	Intervention Exercise group ($n = 52$)	Health education group ($n = 53$)	Excluded ($n = 91$)	P-value‡
Age (years)	77.83 ± 4.21	77.83 ± 4.15	79.55 ± 4.70	0.027
Height (cm)	148.99 ± 5.40	148.18 ± 5.90	147.49 ± 5.65	0.314
Bodyweight (kg)	47.30 ± 7.26	51.74 ± 7.45	48.80 ± 9.25	0.021
BMI (kg/m^2)	21.31 ± 3.07	23.57 ± 3.16	22.33 ± 3.44	0.002
BMD (g/cm^2)	0.27 ± 0.05	0.31 ± 0.06	0.27 ± 0.07	0.083
Grip strength (kg)	17.43 ± 4.77	18.23 ± 4.58	17.62 ± 4.50	0.648
Knee extension strength (kg)	53.27 ± 12.91	54.26 ± 18.77	49.27 ± 14.54	0.522
Dorsiflexion strength (kg)	10.40 ± 2.79	10.49 ± 3.02	8.66 ± 2.98	0.004
Usual walking speed (m/s)	1.19 ± 0.22	1.16 ± 0.23	1.04 ± 0.30	0.002
Maximal walking speed (m/s)	1.84 ± 0.38	1.76 ± 0.48	1.62 ± 0.46	0.031
One leg standing time (s)	32.67 ± 24.27	29.62 ± 23.38	26.25 ± 23.22	0.284
Repeated falls, yes (%)	21.2	11.3	28.6	0.054
Injurious Falls, yes (%)	69.2	79.2	74.7	0.499
Fracture, yes (%)	9.6	9.4	12.1	0.845
Fear of falling, yes (%)	76.9	86.5	84.6	0.368
Urinary incontinence, yes (%)	50.0	52.8	44.0	0.393
Chronic medical conditions, yes (%)				
Hypertension	57.7	43.4	53.8	0.306
Stroke	5.8	9.4	7.7	0.779
Osteoporosis	28.8	24.5	26.4	0.881

†Data are presented as mean and standard deviation for continuous variables, and percentage for categorical variables. ‡One-way analysis of variance for continuous variables and chi-square test for categorical variables. BMI, body mass index; BMD, bone mineral density.

Table 2 Comparison of functional fitness between exercise, education, and excluded participants after 3-month interventions and the 1-year follow up

Variables†	Group	Baseline	After 3-month intervention	After 1-year follow up	ANOVA G × T	P-value
One leg standing time (s)	Exercise	33.71 ± 24.12	36.91 ± 24.79	30.06 ± 22.93	$F = 4.069$	0.020
	Education	32.43 ± 23.45	29.06 ± 23.52	29.26 ± 24.14		
	Excluded	29.87 ± 22.59	24.54 ± 19.06	19.24 ± 17.85		
Usual walking speed (m/s)	Exercise	1.22 ± 0.23	1.28 ± 0.31	1.14 ± 0.25	$F = 8.493$	<0.001
	Education	1.21 ± 0.22	1.26 ± 0.22	1.12 ± 0.22		
	Excluded	1.13 ± 0.24	1.06 ± 0.26	1.03 ± 0.24		
Maximum walking speed (m/s)	Exercise	1.88 ± 0.31	1.86 ± 0.35	1.88 ± 0.34	$F = 2.781$	0.067
	Education	1.84 ± 0.51	1.83 ± 0.35	1.71 ± 0.38		
	Excluded	1.67 ± 0.45	1.68 ± 0.46	1.69 ± 0.50		
Grip strength (kg)	Exercise	17.71 ± 3.87	16.71 ± 4.55	20.06 ± 3.77	$F = 1.746$	0.180
	Education	18.97 ± 4.66	17.86 ± 4.59	20.86 ± 4.65		
	Excluded	18.64 ± 3.75	19.19 ± 3.57	19.50 ± 3.79		
Knee extension strength (kg)	Exercise	55.13 ± 11.00	58.15 ± 13.38	56.01 ± 13.99	$F = 3.812$	0.025
	Education	55.48 ± 15.08	54.70 ± 13.09	51.48 ± 13.99		
	Excluded	53.61 ± 10.35	51.67 ± 11.05	48.68 ± 13.87		
Dorsiflexion strength (kg)	Exercise	10.36 ± 2.71	11.09 ± 3.46	9.88 ± 2.59	$F = 9.542$	<0.001
	Education	10.41 ± 3.01	9.84 ± 2.11	8.81 ± 2.27		
	Excluded	9.01 ± 2.64	8.94 ± 2.80	7.33 ± 3.50		

†Data are presented as mean and standard deviation. ANOVA, two-way analysis of variance; G, group; T, time.

Table 3 Incidence of fall-related variables during 1-year follow up

Variables†	Exercise	Education	Excluded	χ^2 value	% (*n*) *P*-value
Falls (%)	19.6 (10)	40.4 (21)	40.8 (29)	7.069	0.029
Repeated falls (%)	20.0 (2)	33.3 (7)	44.8 (13)		0.329‡
Injurious falls (%)	80.0 (8)	61.9 (13)	72.4 (21)	1.212	0.546
Fractures (%)	10.0 (1)	9.5 (2)	27.6 (8)		0.043‡

†Data are presented as percentage (%) and number of participants (*n*). ‡Fisher's exact test.

Table 4 Adjusted odds ratio for fall-related variables during the 1-year follow up

Independent Variable	Dependent variable: Falls OR	95% CI	Repeated falls OR	95% CI	Injurious falls OR	95% CI	Fractures OR	95% CI
Exercise	1.00		1.00		1.00		1.00	
Education	2.78	1.17–6.96	1.85	0.33–7.38	0.82	0.22–3.05	2.34	0.26–6.57
Excluded	2.83	1.25–6.80	3.22	0.63–8.36	1.94	0.36–7.24	4.30	1.02–9.70

Falls: 1 = yes, 0 = no; Repeated falls: 1 = more than two falls, 0 = one fall; Injurious falls: 1 = yes, 0 = no; Fractures: 1 = yes, 0 = no. OR, odds ratio; CI, confidence interval.

high-risk population. The 3-month exercise intervention provided for the elderly fallers significantly reduced the fall rate, supporting previous findings.[7–10,13,20–22]

There are several factors that can explain the decreased fall rate observed in the exercise group. First is an increase in muscle strength. Previous studies have reported that muscle weakness is a major risk factor for falls,[19,23] and the literature agrees that by strengthening the muscles and improving balance, exercise can prevent falls that cause fractures.[5–7,9,10,13,20,24]

As several studies have shown that approximately 40% of falls occur because of decreased toe clearance,[25–27] the exercise intervention in the present study focused on strengthening the tibialis anterior muscle, which assists ankle dorsiflexion while walking. As shown in Table 2, ankle dorsiflexion strength in the intervention group significantly increased after 3 months of exercise, and decreased slightly (3.9%) during the follow-up period; however, continuous decreases in ankle dorsiflexion strength were observed in both the education (15.4%) and the excluded (18.6%) groups throughout the study period. Similarly, knee extension strength also increased significantly in the exercise group compared with the education and excluded groups, and these gains were maintained even after the 1-year follow up. The increases in ankle dorsiflexion strength and knee extension strength in the exercise group might have had an effect on the observed lower fall rates compared with the education and excluded groups.

The second factor that could explain the decrease in fall rate is improvement in balance.[28] According to the Frailty and Injuries: Cooperative Studies of Intervention Techniques study,[21] balance training by Tai Chi was the most effective method in preventing falls in the elderly. In our trial, five basic forms of Tai Chi that have been shown to improve balance and muscular strength were instructed.[12] The results from the one leg standing time[29] showed that balance significantly increased in the exercise group after the 3-month intervention. In the education and excluded groups, a significant decrease in balance, measured by one-leg standing time, was observed.

Fractures resulting from accidental falls are associated with high mortality rates and increased morbidity.[30] Several previous studies have concluded that exercise can reduce fall-related fracture risk in the elderly population.[4,31,32] Interestingly, in the present study, baseline data showed that BMD between the exercise group (0.265 ± 0.046 g/cm^2) and excluded group (0.271 ± 0.069 g/cm^2) were not significantly different (Table 1); however, the fracture ratio was significantly higher in the excluded group (OR 4.30, 95% CI 1.02–9.70). One explanation that might account for lower fracture rates in the exercise group, despite similar baseline BMD, is improvements in functional ability including muscle strength and balance achieved through exercise.

Another point of discussion is the fall-related characteristics of the excluded people. Although those who are typically excluded from fall prevention trials are at high risk of falling and are prime participants for fall prevention programs, many are excluded based on the exclusion criteria set by researchers for control and safety purposes. In the current study, the fall rate in the

excluded group was quite high, at over 40%. Despite the significantly poorer fitness status in the excluded group observed throughout the study period (Table 1; Table 2), comparison between the excluded group and the education group showed little statistically significant differences after the 1-year follow up not only in fall rate, but in ankle dorsiflexion strength and knee extension strength as well. One explanation for the lack of significance could be due to the 22.0% dropout rate (20 people) in the excluded group (Fig. 1). Although there were no significant differences in repeated falls, and injurious falls between the exercise, education and excluded groups, the fracture rate was significantly higher in the excluded group compared with the exercise group.

There were several limitations in the present study. First, the fall rate assessment was based on subjective data. Examination of fall incidences in the previous year has been reported to be a valid method of determining fall rate.[33] In the present study, we distributed fall diaries to the participants, and instructed them to record any falls and injuries resulting from those falls in an effort to obtain accurate fall data, and subjective data that could not be verified by objective means. Second, the results do not distinguish whether the falls were caused by declines in functional fitness, disease or environmental factors. Third, for various reasons, 22.0% (20 people) of the excluded group were not included in the follow-up data analysis. The missing 22.0% had a large impact on the results, and these factors need to be considered in the interpretation of the results.

The results of the present study showed that an exercise intervention can decrease the rate of falls and fractures in community-dwelling elderly women who have experienced falls at least once in the previous year; however, fracture incidences in excluded people were high. In order to reduce falls in the community-dwelling elderly population as a whole, future research should consider shifting the sole focus from trial participants, to also address people who have been excluded from interventions, as they comprise a large portion of the population who are at high risk of falls and fractures.

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Disclosure statement

The authors declare no conflict of interest.

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Reference Values and Age and Sex Differences in Physical Performance Measures for Community-Dwelling Older Japanese: A Pooled Analysis of Six Cohort Studies

Satoshi Seino[1,2], Shoji Shinkai[1]*, Yoshinori Fujiwara[1], Shuichi Obuchi[1], Hideyo Yoshida[1], Hirohiko Hirano[1], Hun Kyung Kim[1], Tatsuro Ishizaki[1], Ryutaro Takahashi[1] on behalf of the TMIG-LISA Research Group[•]

1 Tokyo Metropolitan Institute of Gerontology, 35-2 Sakae, Itabashi, Tokyo, Japan, 2 The Japan Society for the Promotion of Science, 8 Ichiban, Chiyoda, Tokyo, Japan

Abstract

Objectives: To determine age- and sex-specific reference values for six physical performance measures, i.e. hand-grip strength, one-legged stance, and gait speed and step length at both usual and maximum paces, and to investigate age and sex differences in these measures among community-dwelling older Japanese adults.

Methods: We conducted a pooled analysis of data from six cohort studies collected between 2002 and 2011 as part of the Tokyo Metropolitan Institute of Gerontology-Longitudinal Interdisciplinary Study on Aging. The pooled analysis included cross-sectional data from 4683 nondisabled, community-dwelling adults aged 65 years or older (2168 men, 2515 women; mean age: 74.0 years in men and 73.9 years in women).

Results: Unweighted simple mean (standard deviation) hand-grip strength, one-legged stance, usual gait speed, usual gait step length, maximum gait speed, and maximum gait step length were 31.7 (6.7) kg, 39.3 (23.0) s, 1.29 (0.25) m/s, 67.7 (10.0) cm, 1.94 (0.38) m/s, and 82.3 (11.6) cm, respectively, in men and 20.4 (5.0) kg, 36.8 (23.4) s, 1.25 (0.27) m/s, 60.8 (10.0) cm, 1.73 (0.36) m/s, and 69.7 (10.8) cm, respectively, in women. All physical performance measures showed significant decreasing trends with advancing age in both sexes (all $P<0.001$ for trend). We also constructed age- and sex-specific appraisal standards according to quintiles. With increasing age, the sex difference in hand-grip strength decreased significantly ($P<0.001$ for age and sex interaction). In contrast, sex differences significantly increased in all other measures (all $P<0.05$ for interactions) except step length at maximum pace.

Conclusion: Our pooled analysis yielded inclusive age- and sex-specific reference values and appraisal standards for major physical performance measures in nondisabled, community-dwelling, older Japanese adults. The characteristics of age-related decline in physical performance measures differed between sexes.

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* E-mail: sshinkai@tmig.or.jp

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Introduction

Physical performance measures (PPMs) such as usual gait speed and hand-grip strength are indicators not only of physical function, but also current and future overall well-being, in older adults [1,2]. Recent systematic reviews and meta- and pooled analyses [3–6] showed that PPMs are effective at predicting adverse health outcomes, e.g. disability [7], institutionalization [8], hospitalization [9], and mortality [10]. A recent case-finding algorithm for sarcopenia [11] also included usual gait speed and hand-grip strength as appropriate screening tools. Thus, there is growing evidence of the importance of maintaining adequate physical performance in later life.

Some studies reported normative or reference values for PPMs [12–19]; however, no published study included age- and sex-specific reference values for multiple major PPMs among Asian adults or Japanese adults. Aoyagi et al. [20] conducted a cross-national comparison of PPMs in Japanese and American women and reported that gait speeds and chair stand times were faster for older Japanese women than for older American women, which

suggests that traditional lifestyles may affect physical performance in later life. Because absolute levels of physical performance may vary between countries, it is difficult to extrapolate reference values from previous studies of Western populations [12–17,19] to older Japanese people. Furthermore, the measuring protocols used for several PPMs, especially gait speed and hand-grip strength, varied considerably between studies and countries, which makes comparison of values difficult [21–24]. Therefore, age- and sex-specific PPM reference values specifically for older Japanese adults should be established using unified measuring protocols.

Collaborative research and the combining of cohort data have recently increased in the area of ageing studies [25]. Although the use of a cross-study approach allows analyses to encompass many geographic areas and much larger samples, there may be problems due to differences between studies in the measurement of variables and the protocols used. However, the Tokyo Metropolitan Institute of Gerontology-Longitudinal Interdisciplinary Study on Aging (TMIG-LISA) Research Group [7,26–30] has regularly assessed one-legged stance with eyes open and usual and maximum gait step length, in addition to hand-grip strength and both usual and maximum gait speeds.

In the present study, we pooled cross-sectional data from cohort studies of the TMIG-LISA to establish reference values for six PPMs (hand-grip strength, one-legged stance with eyes open, and gait speed and step length at both usual and maximum paces), classified by age and sex. In addition, we investigated age and sex differences in these measures.

Methods

Data sources and study population

The data sources for this study were derived from the TMIG-LISA [7,26–30], which was established to determine risk factors for participants with geriatric diseases or chronic medical conditions and to identify factors that accelerate or decelerate aging in representative samples of older Japanese adults. In the present study, six TMIG cohort studies contributed data to a pooled analysis: the Nangai Cohort Study (NANGAI), Itabashi Cohort Study 2002 (ITABASHI02), Yoita Longitudinal Study (YOITA), Kusatsu Longitudinal Study (KUSATSU), Hatoyama Cohort Study (HATOYAMA), and Itabashi Cohort Study 2011 (ITABASHI11). We used baseline data or data from the year with the highest participation rate, all of which were collected between 2002 and 2011. The details of the study participants are discussed below (Figure 1).

Nangai Cohort Study (NANGAI). Nangai village is a mainly agricultural area in the northern Japanese prefecture of Akita [31]. The baseline survey was held from July through August 1992, and the participant selection process is described in more detail elsewhere [7,26,28,29]. In the present pooled analysis, we used surveillance data from 2002. The target population included 1327 residents (549 men, 778 women) aged 65 years or older. A total of 1068 ambulatory residents participated in the 2002 survey (446 men, participation rate of 81.2%; 622 women, participation rate of 79.9%; total participation rate of 80.5%).

Itabashi Cohort Study 2002 (ITABASHI02). For ITABASHI02, a baseline survey was conducted in Itabashi ward in north-west Tokyo, Japan in 2002. Two thousand residents (1000 men, 1000 women) aged 71 years or older living in 36 residential areas in Itabashi ward were randomly recruited. After excluding 55 people who were institutionalized, 1945 invitations for the comprehensive health checkups were sent out. Ultimately, 847 residents participated in the baseline survey (456 men, participation rate of 45.6%; 391 women, participation rate of 39.1%; total participation rate of 43.5%).

Yoita Longitudinal Study (YOITA). The Act on Assurance of Medical Care for Elderly People, which went into effect in Japan in 1983, requires all municipal governments in Japan to offer annual preventive health checkups to citizens aged 40 years or older. In conjunction with this service, we launched a longitudinal study on the aging and health of older adults living in Yoita town, a rural community in central Niigata Prefecture, Japan, in which older participants underwent an additional comprehensive geriatric assessment [32]. A total of 1380 residents (521 men, 859 women) aged 70 years or older were invited to participate in a baseline survey in 2004. Of those, 637 residents participated in the survey (261 men, participation rate of 50.1%; 376 women, participation rate of 43.8%; total participation rate of 46.2%).

Kusatsu Longitudinal Study (KUSATSU). We also conducted a longitudinal study in Kusatsu town, a rural community in north-west Gunma Prefecture, Japan, in 2002 [32]. We used data from health checkups conducted in 2008. The study targeted National Health Insurance subscribers aged 65–74 years and individuals 75 years or older in the Medical Insurance System for the Elderly Aged 75 or Over (966 men, 1219 women). Of that population, 665 residents participated in the 2008 survey (276 men, participation rate of 28.6%; 389 women, participation rate of 31.9%; total participation rate of 30.4%).

Hatoyama Cohort Study (HATOYAMA). The HATOYAMA study was a prospective cohort study of community-dwelling people aged 65 years or older living in the town of Hatoyama in Saitama Prefecture, Japan. The full details of the participant selection process were previously published [33]. Briefly, 2697 residents (1354 men, 1343 women) aged 65–84 years were selected using stratified sampling classified by age and residential area and random sampling strategies. Of those, 751 people participated in a baseline survey in 2010 (participation rate of 27.8%). Ultimately, 9 persons declined to participate in the study, and a total of 742 people were included in the study (428 men, participation rate of 31.6%; 314 women, participation rate of 23.4%; final participation rate of 27.5%).

Itabashi Cohort Study 2011 (ITABASHI11). In the ITABASHI11 study, 7162 residents aged 65–84 years living in nine residential areas surrounding the TMIG were recruited in 2011. After excluding 463 people who were institutionalized or overlapped from previous studies, 6699 invitations (3136 men, 3563 women) for the health checkups were sent out. In October 2011, 913 ambulatory residents received health checkups (participation rate of 13.6%) [30]. Of those, 905 residents agreed to participate in the study (361 men, participation rate of 11.5%; 544 women, participation rate of 15.3%; final participation rate of 13.5%).

Final sample size. Of all the participants (n = 4864) in the pooled data of the present study, individuals were excluded if they were not independent in any of five basic activities of daily living (ADLs), i.e. bathing, dressing, walking, eating, and continence [7] or had data missing for all PPMs. We also excluded four participants in the HATOYAMA study because their PPMs were measured at their homes. The final, pooled sample size was 4683 (2168 men and 2515 women; 28.8% and 28.7%, respectively, of the target population). All participants provided written informed consent, and all studies included in the pooled analysis were conducted with the approval of the institutional review board and ethics committee of the TMIG.