Table 4 Prevalence of BPSD and median of the median distance moved per day according to the presence or absence of BPSD in descending order of prevalence (n = 28)

NPI-NH subscales	Prevalence of BPSD (%)	Median of the median distance moved per day (m)		
		BPSD (+)	BPSD (–)	P-value†
Agitation	50	3667	2695	0.71
Apathy	39	2317	3190	0.94
Irritability	36	4628	1858	0.70
Aberrant motor behaviour	32	4572	2030	0.77
Night-time behaviours	32	4649	1994	0.08
Appetite changes	32	3495	2706	0.63
Disinhibition	21	4991	2262	0.042†
Delusions	18	1527	3134	0.17
Hallucinations	18	2868	2843	0.12
Depression	11	4714	3189	0.20
Anxiety	7	2091	2905	0.67
Euphoria	7	6570	2547	0.17

† Wilcoxon rank sum test. BPSD, behavioural and psychological symptoms of dementia; NPI-NH, Neuropsychiatric Inventory Nursing Home Japanese version.

Association between the median distance moved per day and BPSD

Of 40 patients, 12 patients were excluded from this analysis because consecutive 7-day monitoring data could not be obtained due to (i) leaving hospital for the weekend or (ii) being isolated in the private room during NPI-NH evaluation period. Of the remaining 28 patients, the median of the median distance moved per day was 2936 m.

The prevalence of BPSD varied greatly (Table 4). Agitation was the most common BPSD, followed by apathy and irritability. Conversely, euphoria and anxiety were the least common BPSD. When the median distance moved per day for those with each positive BPSD was compared with those with negative BPSD, only disinhibition reached statistical significance (Table 4).

DISCUSSION

The current study found a wide variation in the median distance moved per day in 40 AD patients measured by the IC tag monitoring system, and age and cognitive function explained 47% of the variance. Severity and duration of dementia, and of the 12 symptoms measured by NPI-NH, only disinhibition was significantly associated with the median distance moved per day.

A major strength of our study was a quantification of wandering in terms of the median distance moved per day in AD patients around the clock for over 2 month period. There are studies which direct observation of dementia patients was used. However, observation per session was short in duration and total duration of observation was mostly few days.[6] Further, scales used to measure wandering were administered by caregivers with various definition of wandering.[12–14] This makes it difficult to compare among studies.

Physical stamina to walk will decrease with advancing age, and our finding is in accordance with this hypothesis. However, previous studies reported contradictory findings. There was an inverse association between age and wandering in a US study,[14] whereas the other multicenter US study reported positive association.[25] In a Taiwanese study no association was found.[10]

These inconsistencies might reflect the differences in the definition and measurement of wandering. All aforementioned studies used different scales to measure BPSDs. In one US study by Colombo *et al.*,[14] aberrant motor behaviour, one of the 12 NPI-NH subscales, was used to measure wandering in institutionalized PWD. Aberrant motor behaviour has seven items which primarily evaluates repetitive activities, and pacing (back

and forth movements) is one of them. In the other US study by Cooper *et al.*, the definition of wandering was not described in the paper whereas reporting patient's age was a positive predictor of wandering ($P < 0.041$) with adjustment for an MMSE ($P < 0.001$) in a logistic model.[25] In the Taiwanese study,[12] BEHAVE-AD was used to measure wandering, in which wandering was defined as 'wandering around the ward or wandering from home or caregiver'.

Cognitive declines are also a predictor of the median distance moved per day in our study, and it is in concordant with all the previous studies.[12–15] Although measurement of wandering differed among studies, these scales measure BPSDs which manifest as the cognitive function decline.

Duration of dementia was expected to be associated with the median distance moved per day; however, this hypothesis was rejected in our study. Progression of AD might differ between those with young onset and those with late onset. Our sample size was too small to control for age at onset of AD. The US study by Cooper *et al.* also found a lack of association between the duration of dementia and wandering.[25] A few factors might explain a lack of association. Firstly, at institutional settings, patients with dementia are admitted for a variety of reasons, which could not be related to the duration of dementia. Secondly, onset of dementia symptoms might not be accurately reported if the patient had not had household members.

Severity of dementia measured by CDR was not associated with the median distance moved per day mainly due to the variability within the group. Further, CDR is a qualitative evaluation of mental function as well as usual activities such as social function and self-care.[23] These activities did not directly relate to the median distance moved per day.

With the exception of disinhibition, the median distance moved per day did not differ significantly between those with and without BPSDs measured by NPI-NH. Some of the subscales related to agitation, such as nighttime behaviour, might have been type 2 error due to the low prevalence.

Our study was limited to the measurement of the median distance moved per day, and other dimensions of wandering were not measured. In the future study, wandering related to care burden needs to be quantified with objective measurement in order to evaluate interventions. There are patients with excessive ambulation, and this group of patients needs to be examined further for appropriateness of the activity levels. These excessive wandering could be related to the region of the brain affected which could be identified with advancing technology. The other limitation is that the patient's movement within their room was not monitored, and our study might have underestimated the ambulation in some patients who tended to move around in their room.

In summary, the IC tag monitoring system was used to describe the degree of ambulation in terms of the median distance moved per day in institutionalized AD patients over a 2 month period, and factors associated with the median distance moved per day were explored. In total, 40 patients were monitored. The median distance moved per day varied from 276 m to 12 336 m, with a median of 1610 m. In a multiple linear regression, patients' age and cognitive function explained 47% of the variance in the median distance moved per day. In terms of BPSD, only disinhibition reached the statistical significance.

CONFLICT OF INTEREST

None.

DESCRIPTION OF AUTHORS' ROLES

The first author analyzed and drafted the paper. The second and third authors implemented the research. The fourth author assisted the logistics and data analysis. The last author supervised the whole project and edited the paper.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation for the contributions of the patients and their families at Asakayama General Hospital. We are especially grateful for the cooperation of the staff of the Hospital. This study was supported by a Grant-in-Aid for Scientific Research (for Young Scientists B, No.20791766, 2008–2010) from Japan's Ministry of Education, Culture, Sports, Science, and Technology.

REFERENCES

1 Kiely DK, Kiel DP, Burrows AB, Lipsitz LA. Identifying nursing home residents at risk for falling. *Journal of the American Geriatrics Society* 1998; **46**: 551–555.

2 Logsdon RG, Teri L, McCurry SM *et al.* Wandering: A significant problem among community-residing individuals with Alzheimer's disease. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences* 1998; **53**: 294–299.

3 Lim YM, Son GR, Song JA, Beattie E. Factors affecting burden of family caregivers of community-dwelling ambulatory elders with dementia in Korea. *Archives of Psychiatric Nursing* 2008; **22**: 226–234.

4 Pellfolk T, Gustafsson T, Gustafson Y, Karlsson S. Risk factors for falls among residents with dementia living in group dwellings. *International Psychogeriatrics* 2009; **21**: 187–189.

5 Robinson L, Hutchings D, Dickinson HO *et al.* Effectiveness and acceptability of non-pharmacological interventions to reduce wandering in dementia: A systematic review. *International Journal of Geriatric Psychiatry* 2007; **22**: 9–22.

6 Yayama S, Yamakawa M, Kutumi M, Makimoto K. Objective measurement of wandering in elderly patients with dementia. In: Mohan RM (ed.). *Research Advances in Age and Aging*. Kerala, India: Global Research Network, 2011; 1–14.

7 Martino-Saltzma D, Blasch BB, Morris RD, McNeal LW. Travel behavior of nursing home residents perceived as wanderers and nonwanderers. *Gerontologist* 1991; **31**: 666–72.

8 Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *Journal of Gerontology* 1989; **44**: M78–M84.

9 Algase DL, Beatie ER, Bogue E, Yao L. The Algase wandering scale: Initial psychometrics of a new caregiver reporting tool. *American Journal of Alzheimer's Disease and Other Dementias* 2001; **16**: 141–152.

10 Cummings JL. The Neuropsychiatric Inventory: Assessing psychopathology in dementia patients. *Neurology* 1997; **48** (5 Suppl. 6): S10–S16.

11 Harwood DG, Ownby RL, Barker WW, Duara R. The behavioral pathology in Alzheimer's Disease Scale (BEHAVE-AD): Factor structure among community-dwelling Alzheimer's disease patients. *International Journal of Geriatric Psychiatry* 1998; **13**: 793–800.

12 Yang CH, Hwang JP, Tsai SJ, Liu CM. Wandering and associated factors in psychiatric inpatients with dementia of Alzheimer's type in Taiwan: Clinical implications for management. *The Journal of Nervous and Mental Disease* 1999; **187**: 695–697.

13 Klein DA, Steinberg M, Galik E, Steele C, Sheppard JM. Wandering behaviour in community-residing persons with dementia. *International Journal of Geriatric Psychiatry* 1999; **14**: 272–279.

14 Colombo M, Vitali S, Cairati K *et al.* Wanderers: Features, findings, issues. *Archives of Gerontology and Geriatrics* 2001; **33** (Suppl. 1): 99–106.

15 Rolland Y, Andrieu S, Cantet C *et al.* Wandering behavior and Alzheimer disease. The REAL.FR prospective study. *Alzheimer Disease Associated Disorders* 2007; **21**: 31–38.

16 Nakaoka A, Suto S, Makimoto K *et al.* Pacing and lapping movements among institutionalized patients with dementia. *American Journal of Alzheimer's Disease and Other Dementias* 2010; **25**: 167–172.

17 Greiner C, Makimoto K, Suzuki M, Yamakawa M, Ashida N. Feasibility study of the integrated circuit tag monitoring system for dementia residents in Japan. *American Journal of Alzheimer's Disease and Other Dementias* 2007; **22**: 129–136.

18 Makimoto K, Eun AL, Kang Y, Yamakawa M, Ashida N, Kyung RS. Temporal patterns of movements in institutionalized elderly with dementia during 12 consecutive days of observation in Seoul, Korea. *American Journal of Alzheimer's Disease and Other Dementias* 2008; **23**: 200–206.

19 Yamakawa M, Suto S, Shigenobu K, Kunimoto K, Makimoto K. Comparing dementia patients' nighttime objective movement indicators with staff observation. *Psychogeriatrics* 2012; **12**: 18–26.

20 Miyoshi R, Yamakawa M, Shigenobu K *et al.* Association between activity level and changes in bodyweight in dementia patients. *Psychogeriatrics* 2008; **8**: 170–174.

21 McKhann G, Drachman D, Folstein M *et al.* Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939–944.

22 Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975; **12**: 189–198.

23 Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 1993; **43**: 2412–2414.

24 Shigenobu K, Hirono N, Tabushi K, Ikeda M. Validity and reliability of the Japanese version of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). *Brain & Nerve/Shinkei Kenkyu No Shinpo* 2008; **60**: 1463–1469.

25 Cooper JK, Mungas D, Weiler PG. Relation of cognitive status and abnormal behaviors in Alzheimer's disease. *Journal of the American Geriatrics Society* 1990; **38**: 867–870.

Psychiatry and Clinical Neurosciences 2014; **68**: 216–224 doi:10.1111/pcn.12127

Regular Article

Multicenter population-based study on the prevalence of early onset dementia in Japan: Vascular dementia as its prominent cause

Chiaki Ikejima, PhD,[1,2] Manabu Ikeda, MD, PhD,[3] Mamoru Hashimoto, MD, PhD,[3] Yusuke Ogawa, MD, PhD,[3] Satoshi Tanimukai, MD, PhD,[4] Tetsuo Kashibayashi, MD, PhD,[5] Kazuo Miyanaga, MD, PhD,[6] Kimie Yonemura, MD, PhD,[7] Tatsuyuki Kakuma, MPH, PhD,[8] Kenta Murotani, PhD[9] and Takashi Asada, MD, PhD[2]*

[1]*Department of Disaster Psychiatry, Faculty of Medicine,* [2]*Department of Neuropsychiatry, Faculty of Medicine, University of Tsukuba, Ibaraki,* [3]*Department of Psychiatry and Neuropathology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto,* [4]*Department of Neuropsychiatry and Neuroscience, Ehime University Graduate School of Medicine, Ehime,* [5]*Hyogo Prefectural Rehabilitation Hospital at Nishi-Harima, Hyogo,* [6]*Yukiguni-Yamato Hospital, Niigata,* [7]*Department of Psychiatry and Neuroscience, Gunma University Graduate School of Medicine, Gunma,* [8]*Department of Biostatistics, Kurume University, Fukuoka, and* [9]*Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Aichi, Japan*

Aim: In Japan, the government and media have become aware of the issues of early onset dementia (EOD), but policies for EOD have not yet been established and support systems are inadequate. To provide practical data about EOD, a two-step postal survey was performed.

Methods: A questionnaire requesting information on EOD cases was sent to target institutions in five catchment areas in Japan. According to the answers from the institutions, we estimated the prevalence of EOD using census data and determined the illnesses causing EOD. As a quality control study, the authors reviewed every diagnosis in a quarter of the reported cases using the medical and psychiatric records and neuroimaging data. This study was conducted from 2006 to 2007.

Results: Information from 2469 patients was collected from 12 747 institutions, and 2059 subjects with EOD were identified. The estimated prevalence of EOD was 47.6 per 100 000 (95% confidence interval, 47.1–48.1) for all of Japan. Of the illnesses causing EOD, vascular dementia (VaD) was the most frequent (39.8%), followed by Alzheimer's disease.

Conclusions: The prevalence of EOD in Japan appeared to be similar to that in Western countries. However, unlike previously reported international experience, VaD was the most frequent cause of EOD in all catchment areas in Japan.

Key words: Alzheimer's disease, early onset dementia, prevalence, vascular dementia.

IN DEVELOPED COUNTRIES, dementia with onset before the age of 65 years, defined as early onset dementia (EOD), has presented a unique challenge to society and those who care for such individuals.[1]

In Japan, although several reports have described the prevalence of EOD and the frequency of illnesses causing EOD, their results differ depending on the study settings. Two university-hospital-based studies reported that the most common dementia diagnosis

Correspondence: Takashi Asada, MD, PhD, Department of Neuropsychiatry, Faculty of Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 305-8575, Japan. Email: tasada@md.tsukuba.ac.jp
Received 18 January 2013; revised 27 August 2013; accepted 10 September 2013.

was Alzheimer's disease (AD).[2,3] On the other hand, one community-based study and one nationwide study, including five catchment areas, reported that the most frequent illness causing EOD was VaD.[4,5] Recently, we reported on a population-based study in a single catchment area with a population of 3 million.[6] Our study revealed also that vascular dementia (VaD) was the most common cause of EOD. Using the same methodology in a much larger population of over 9 million, we estimated the prevalence of EOD and examined the prominence of VaD among illnesses causing EOD.

METHODS

This study was conducted in five catchment areas in Japan: Ibaraki (population, 3 million), Gunma (2 million), Toyama (1 million), Ehime (1.5 million) and Kumamoto (1.8 million). These areas are representative of Japan's geographic, economic and educational composition. The productive-age population ratio of all Japan was 65.5 in 2006 and 65.0 in 2007, and in those five areas the average was 63.1 (range 61.3–66.0). Therefore, in order to reduce the influence of biased sample populations, prevalence in each area was adjusted using the standardized population. EOD subjects were defined as those whose age at onset and age on the census day was less than 65 years. The observation period in each area was 6 months: from 1 April to 31 October 2006 for Ibaraki and Gunma, from 1 April to 31 October 2007 for Toyama, and from 1 July to 31 December 2007 for Ehime and Kumamoto (Fig. 1). The reason why this period was employed was to allow direct comparison with a previous Japanese EOD study, which used 6 months.[5]

The survey was approved by the local ethics committees, including those of the University of Tsukuba, Kumamoto University, Ehime University, Gunma University, and Toyama Medical Association.

Step 1

A questionnaire was mailed to all of the following: medical institutions (including psychiatric and neurological hospitals and clinics), home-visit nursing services, long-term care insurance (LTCI)-related facilities, local branches of prefectural health, and local welfare commissioners. In Japan, all care services for community-dwelling individuals with EOD are provided by a publicly funded LTCI, which is separate from medical care insurance.

Each institution was asked, 'How many EOD patients did you care for in the last 6 months?' The criteria for the diagnosis of dementia were based on the DSM-III-R.[7]

Step 2

For the second step, respondent institutions with one or more cases were asked to provide additional patient data, including: initials, demographics, coexisting illnesses, duration and type of dementia, illnesses causing dementia (in the case of VaD, specifying the subtype of cerebrovascular disease [CVD]), severity of dementia, and functional status. Patients were then classified into subgroups according to the cause of dementia. AD, vascular dementia and alcohol-related dementia were defined according to the DSM-IV.[8] It is noteworthy that, in contrast to other VaD criteria, including National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences,[9] the DSM-IV criteria for VaD requires neither temporal relation between dementia and recognized stroke nor progressive cognitive decline. Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) were diagnosed according to the revised criteria for the clinical diagnosis of dementia with Lewy bodies,[10] and frontotemporal lobar degeneration (FTLD) was diagnosed according to the Lund and Manchester Criteria.[11] Finally, patients fulfilling the DSM-III-R criteria for dementia but not fulfilling criteria for any of the above diagnostic categories were designated 'Other'. Individuals with two or more comorbid diseases causing dementia, such as AD with VaD, were classified as 'overlap' and included in the 'Other' category.

The age at onset of disease was defined as the age of the patient at which the earliest conclusive dementia symptom was noticed by caregivers or other close informants.

Determination of dementia severity was based on the original manuals used by a previous Japanese EOD study[5] for comparison. Three stages of severity were defined as follows. Mild: the person can mostly live independently, with adequate personal hygiene and relatively intact judgment, but social activities and employment are both significantly impaired. Moderate: independent living is fraught with hazard to the extent that supervision is required. Severe: there is severe impairment of daily activities and continual supervision is needed.

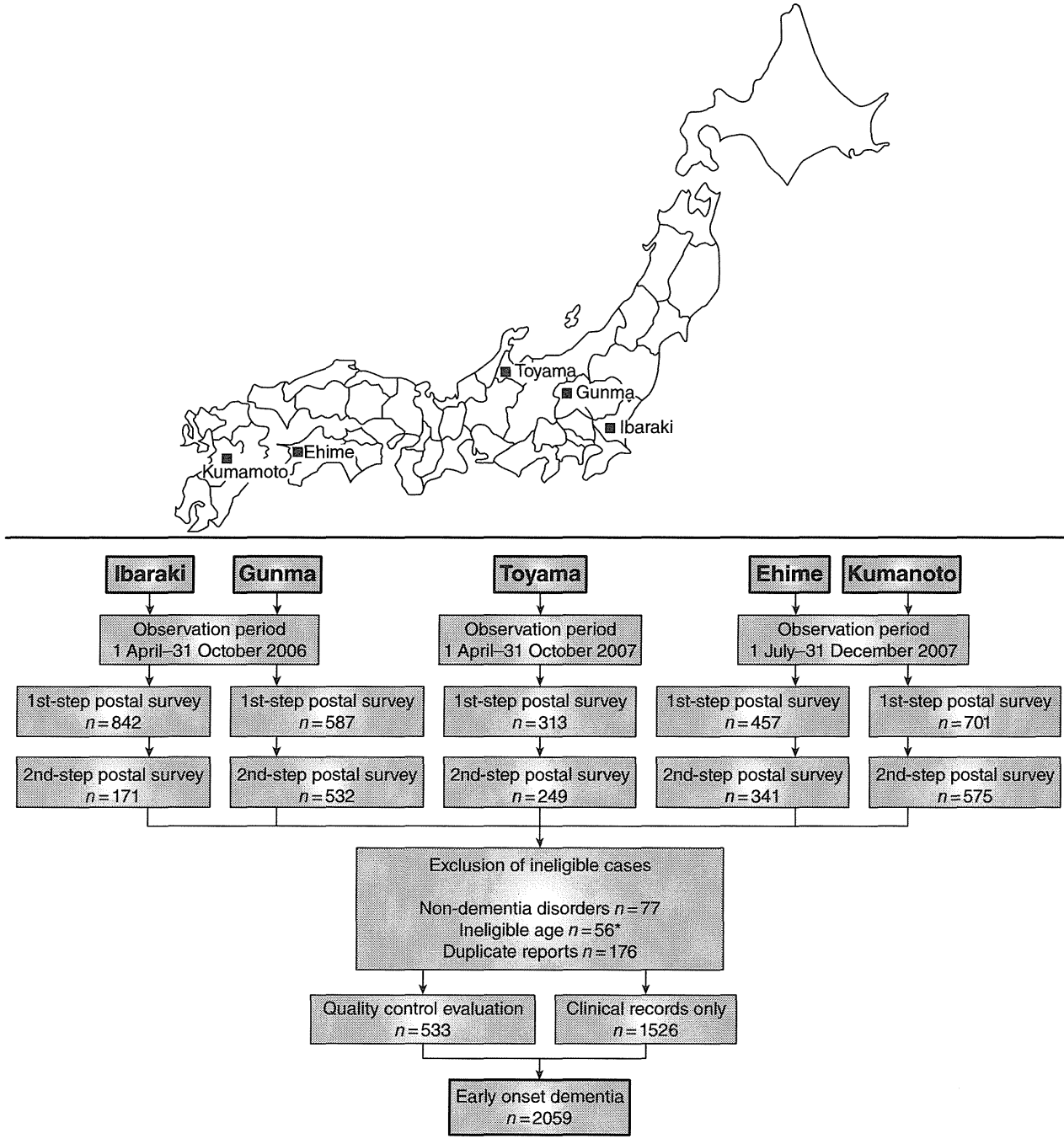

Figure 1. Map of Japan and schedule of each catchment area's survey.

Answers to the additional information for reported cases from non-medical institutions were based on comments by the consulting physicians.

It should be noted that in Japan acute illnesses, including stroke, are diagnosed and managed initially in hospitals then intensive rehabilitation units, prior to discharge home or to longer-term care in LTCI institutions. Degenerative illnesses are usually managed in specialist hospital outpatient clinics, prior to LTCI institutions for advanced stages. Hence,

almost all patients in this study would have received specialist evaluation at some stage of their illness, and hence their assigned diagnoses should be clinically accurate.

Quality control

In order to validate the accuracy of reported diagnoses, we conducted a quality control (QC) study using data from a quarter of the reported cases. We selected the institutions for this sub-study in descending order of reported case numbers. The authors of this paper visited such institutions and reviewed the patients' medical and psychiatric records and neuroimaging data, including magnetic resonance imaging (MRI), computed tomography (CT) and single photon emission computed tomography (SPECT). A separate diagnosis was made independently for each subject. In this way, the accuracy of the diagnosis of the attending physician from each institution could be evaluated.

Statistical analysis

The data to estimate the prevalence are based on the last governmental reports before the start of the observation period. The reports were published on 1 April 2006 for Ibaraki, on 1 October 2006 for Gunma and on 1 October 2007 for Toyama, Ehime, Kumamoto and the whole of Japan. The population denominators used were derived from census data of the target areas.

In each area, in order to reduce sampling bias due to case reporting failures, we adjusted using the response rates. The reciprocal of the product of the response rate for steps 1 and 2 (sample weight) was calculated, and the number of EOD patients was estimated using the sample weight multiplied by the reported number of cases as follows.

n_{ij} = reported number of dementia cases by area i and age strata j

w_i = sampling weight of area $_i$

P_{ij} = population of area i and age strata j.

We defined the estimated number of dementia cases of area i, age strata j as $m_{ij} = w_i n_{ij}$.

and the estimated prevalence per X as $\hat{\lambda}_{ij} = \frac{m_{ij}}{P_{ij}} X$.

Then, the estimated prevalence was adjusted by the standardized population, and the weighted average prevalence was calculated for the purpose of reducing the influence of different population distributions as follows.

Tj = all Japan population of age strata j at study period $S_j = \frac{Tj}{\sum_j Tj}$.

The estimated prevalence adjusted by the standardized population in area i was obtained by $\hat{T}_i = \sum_j S_j \hat{\lambda}_{ij}$.

We defined the population of area i as $Pi = \sum_j P_{ij}$.

The weighted average prevalence was obtained by $\hat{T} = \sum_i \Phi_i \hat{T}_i$

and $\Phi_i = \frac{\sum_j P_{ij}}{\sum_{ij} P_{ij}}$.

The EOD prevalence for the total Japanese population was estimated by integration of the adjusted prevalence in the five catchment areas. We regarded this prevalence as the Japanese standardized prevalence.

We calculated 95% confidence intervals (CI) based upon a standard normal distribution. The significance of differences between rates was estimated by χ^2-test or Fisher's exact tests. All analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC, USA) and R version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

As shown in Table 1, information from 2469 patients was collected from 12 747 institutions. Approximately 50% of the diagnoses were made in hospitals or clinics, and only 10% by general practitioners. For the remaining cases mainly cared for in LTCI institutions, diagnoses were made by either specialists or general practitioners to consider the appropriateness of their admission before the patients moved into their LTCI institutions.

After careful review of the answer sheets, patients with the following diagnoses were excluded: schizophrenia ($n = 8$), developmental disorder ($n = 38$), depression ($n = 6$), and other non-dementia disorders ($n = 25$). None of these patients were considered to have had concomitant EOD. Fifty-six patients were excluded because their age on the census day was over 65, although their age at onset of dementia was less than 65.

We received reports from two or more institutions for the same 157 cases. Consequently, 176 reports for

Table 1. Response rates of the postal surveys

Institutions	Step 1			Step 2			
	Target population	$n^{\dagger}$	Response rate (%)	Target population	$n^{\dagger}$	Response rate (%)	Reported cases
Hospitals	1 489	1 231	(82.7)	254	210	(82.7)	1429
Clinics	5 573	4 622	(82.9)	151	119	(78.8)	276
Health service facilities	385	326	(84.7)	95	81	(85.3)	185
Special nursing homes	919	847	(92.2)	137	112	(81.8)	214
Group homes	812	733	(90.3)	97	78	(80.4)	123
Welfare service center for disabled people	464	427	(92.0)	12	11	(91.7)	115
Day center	362	332	(91.7)	45	37	(82.2)	66
Home-visit nursing facilities	488	266	(54.5)	38	35	(92.1)	62
Welfare living centers	356	316	(88.8)	47	42	(89.4)	80
Government services	156	139	(89.1)	13	12	(92.3)	90
Local welfare commissioners	201	186	(92.5)	14	9	(64.3)	28
Care managers	1 542	1 156	(75.0)	174	147	84.5)	233
Total	12 747	10 582	(83.0)	1077	893	(82.9)	2901

†Number of respondent institutions.

the 157 cases were excluded. Among these cases, nine received different diagnoses according to the informants: AD and DLB for four cases, AD and brain infection for one, AD and Behçet's disease for one, AD and FTLD for one, AD and alcohol-related dementia for one, and VaD and alcohol-related dementia for one. Overall percent agreement of diagnosis for the 157 doubly or triply reported cases was 95.1%, and the percent for 40 of the 157 patients with diagnosis of VaD was as high as 97.5%.

For the cases lacking diagnostic agreement, we prioritized the diagnoses according to the following order: diagnosed by neurologists or psychiatrists at general hospitals, including university hospitals; diagnosed by psychiatrists or neurologists; diagnosed by physicians at general hospitals; diagnosed by physicians at clinics; and diagnosed by physicians from other health-care facilities. The final sample population comprised 2059 subjects (61.0% male). The mean age and age at dementia onset on the census day were 56.4 years (SD, 8.0; range, 18–64 years) and 51.3 years (9.8; 18–64 years), respectively.

As shown in Figure 2, of the illnesses causing EOD, VaD was the most frequent (40.1%), followed by AD (24.3%), head trauma (8.4%), FTLD (3.6%), alcohol-related dementia (3.2%), DLB/PDD (2.8%) and others (14.2%). The 'Other' category included seven subcategories: dementia secondary to neurodegenerative disorders (4.4%), for example, spinocerebellar degeneration, multiple system atrophy and progressive supranuclear palsy; infection (3.1%); surgery for brain tumor (1.9%); hypoxia (1.4%); other organic brain syndrome (2.9%), for example, normal pressure hydrocephalus and epilepsy; unknown dementia (3.4%); and overlap (0.5%). Six patients with both AD and VaD were included in the overlap category. The main subtypes of VaD were single large infarction (37.3%), intra-cerebral hemorrhage (35.7%), and subarachnoid hemorrhage (18.6%) (Fig. 2). Table 2 shows the prevalence rate of AD and VaD by sex for each catchment area. The most frequent illness causing EOD was VaD for men in all catchment areas, and AD for women in four areas. There was no significant difference in the distribution of VaD and AD for both sexes among the catchment areas. The prevalence of dementia in terms of dementia severity and the ratio for living places are shown in Table 2.

The QC evaluations were performed for 545 EOD individuals (26.5%). The percentage of agreement between the authors and doctors at the selected institutions for diagnosis of overall dementia was 98.9% and for VaD, it was 100%. The frequency of illnesses

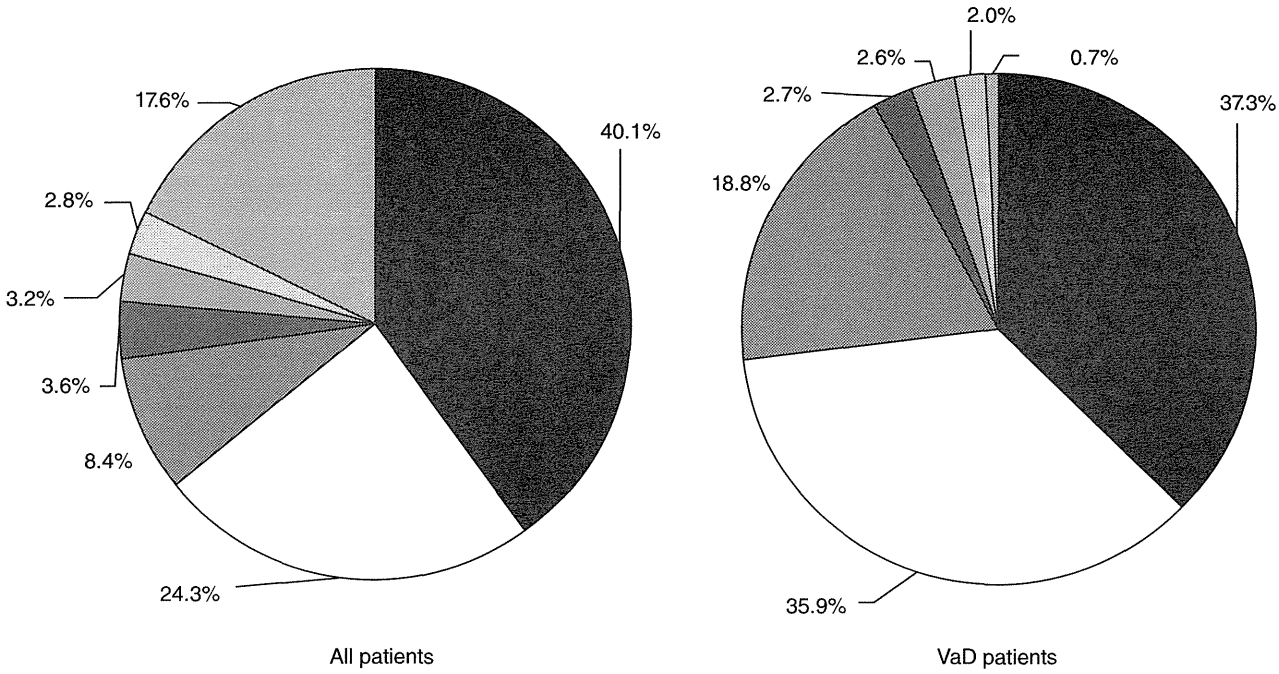

Figure 2. Distribution of diagnoses. All patients: (■) vascular dementia (VaD); (□) Alzheimer's disease; (▨) Head trauma; (▩) frontotemporal lobar degeneration; (▨) alcohol-related dementia; (▨) dementia with Lewy bodies/Parkinson's disease with dementia; and (▨) Others. VaD patients: (■) Large cortical infarct; (□) Cerebral hemorrhage; (▩) Subarachnoid hemorrhage; (▩) Unspecified; (▨) Mixed cerebrovascular disease; (▨) Multiple infarction; and (▨) Others.

causing EOD was calculated for two subgroups among the target individuals: university hospitals ($n = 252$) and others ($n = 293$). There were significant differences between the two groups ($P < 0.0001$): higher frequencies of AD (46.0%) and DLB (11.9%) and lower frequencies of VaD (6.3%) for the university hospital group. We reviewed CT or MRI images for 26.5% of patients during the 6-month study period and 18.6% after 6 months retrospectively because we offered quality control after we received the reports from institutions.

The total estimated number of patients adjusted by the standardized population of Japan was calculated to be 37 800. The prevalence rate in those aged 18–64 years was 47.6 per 100 000 (95%CI, 45.5–49.7). From the age of 30 onwards, the prevalence rate of dementia approximately doubled with each 5-year increase in age (Table 3).

DISCUSSION

To our knowledge, this is the largest population-based epidemiological study targeting EOD. There was no significant difference between our study and those from Western countries (Table 4) in the prevalence of all types of EOD combined.[4,5,12–17]

The proportion of illnesses causing EOD was quite different from the UK. Harvey *et al.*[16] reported causes there as AD 34%, VaD 18%, FTLD 12%, DLB 7%, alcoholic dementia 10%, and others 19%. Ratnavalli *et al.*[15] reported that primary degenerative dementias accounted for 71%, of which 35% were AD and 22% were FTLD. Namely, our study showed prominence of VaD, especially in men.

A nationwide study of Japanese EOD prevalence in 1997 also reported a higher prevalence of VaD (43.9%) than AD (16.8%).[5] The Strategies against Stroke Study for Young Adults in Japan (SASSY-Japan) used data from 7245 stroke patients from 18 centers and compared the salient features of stroke in younger (<50 years old) and older groups (<51 years old).[18] The SASSY-Japan study reported that male sex was a risk factor for the younger group. Even in Western countries, men have higher stroke prevalence than women, especially at young ages.[19]

Table 2. Comparison of five catchment areas

	Total	Ibaraki	Gunma	Toyama	Ehime	Kumamoto	*P*-value
Total population (all ages)	9 370 651	2 965 931	2 019 120	1 105 312	1 452 000	1 828 288	–
Target population aged 18–64 years, male (%)	5 664 741 (50.2)	1 862 942 (51.2)	1 238 395 (50.9)	654 646 (50.3)	848 641 (49.1)	1 060 137 (48.6)	–
Estimated number of patients	2 965	761	748	258	504	694	–
Prevalence† for age range 18–64	52.4	40.8	60.4	39.4	59.4	65.5	–
Prevalence† for age range 45–64	103.2	83.3	121.0	81.6	114.7	120.8	–
Prevalence† of AD and VaD by sex							
Male							
VaD	26.0	23.5	40.2	14.6	29.5	29.8	0.012
AD	9.7	9.0	11.8	12.1	14.3	8.0	0.448
Female							
VaD	11.9	12.0	14.1	7.4	12.6	16.7	0.675
AD	13.4	12.9	16.7	13.4	11.9	17.7	0.779
Both sexes							
VaD	19.1	18.1	27.4	11.0	21.3	23.1	0.113
AD	11.6	10.9	14.2	12.8	13.1	13.0	0.978
Severity of dementia							
Mild	24.3%	25.3%	24.3%	19.0%	22.8%	25.0%	–
Moderate	33.2%	29.0%	36.3%	29.9%	32.6%	37.9%	–
Severe	35.5%	36.0%	34.5%	46.0%	39.2%	29.4%	–
Living places							
Hospitalized and institutionalized	29.4%	36.8%	21.2%	30.8%	47.2%	35.8%	–
Living at home	38.3%	47.5%	62.1%	42.2%	40.5%	59.1%	–
Missing	32.3%	15.7%	16.7%	27.0%	12.3%	5.1%	

†Prevalence per 100 000 population.
AD, Alzheimer's disease; VaD, vascular dementia.

Although several explanations, including the role of estrogen, have been proposed, the true reason why Japanese men are more vulnerable to stroke than women remains an open question. At any rate, the high frequency of VaD in men accounts for the main result. On the other hand, it should be noted that AD prominence in women was observed in four of the five areas. Another important issue is the difference between presenile and senile populations in Japan in the pathogenesis of VaD. The SASSY-Japan reported that cerebral and subarachnoid hemorrhage were the major cause of presenile stroke, whereas lacunar infarction was the major cause in senile stroke victims. Our study also revealed that cerebral and subarachnoid hemorrhage were the major cause of EOD. Additionally, a population-based study of persons aged 65 years and older in a Japanese community found that the most frequent illness causing VaD was multiple lacunar infarction.[20] Taken together, the causes of stroke in the younger population appear to be quite different from those affecting the older population.

Our QC study and the examination of doubly or triply reported cases showed a high concordance between the diagnosis of illnesses causing EOD in general and VaD in particular. The QC also revealed that the most common EOD-causing illness was AD for all of the five university hospitals, which replicated the results of previous university-hospital-based EOD studies in Japan.[2,3] On the other hand, VaD was the leading cause for patients in the non-university hospitals. Considering the above-described Japanese medical system for acute and degenerative illnesses, this difference may be understandable. A possible reason for the discrepancy between the university-hospital-based diagnoses and those in other institu-

Table 3. Prevalence of early onset dementia in Japan

Japanese population (thousands)			All causes of dementia			Male			Female		
Age range, years	Total	Male	Female	$n^{\dagger}$	Prevalence	95%CI[‡]	n	Prevalence	95%CI	n	Prevalence	95%CI
18–19	2 618	1 341	1 277	21.6	0.8	(0.5–1.3)	21.9	1.6	(1.1–2.5)	0.0	0.0	0.0–0.3
20–24	7 238	3 716	3 521	367.3	5.1	4.6–5.6	289.5	7.8	6.9–8.7	78.6	2.2	1.8–2.8
25–30	7 795	3 967	3 828	451.6	5.8	5.3–6.4	330.5	8.3	7.5–9.3	120.3	3.1	2.6–3.8
30–34	9 363	4 748	4 615	552.6	5.9	5.4–6.4	434.9	9.2	8.3–10.1	117.0	2.5	2.1–3.0
35–39	9 426	4 763	4 663	839.8	8.9	8.3–9.5	539.2	11.3	10.4–12.3	301.8	6.5	5.8–7.2
40–44	8 220	4 141	4 079	1 218.4	14.8	14.0–15.7	766.3	18.5	17.2–19.9	455.6	11.2	10.2–12.2
45–49	7 733	3 879	3 854	2 094.9	27.1	26.0–28.3	1 303.7	33.6	31.8–35.5	795.5	20.6	19.3–22.1
50–54	8 051	4 018	4 033	4 163.6	51.7	50.2–53.3	2 737.3	68.1	65.6–70.7	1 407.9	34.9	33.1–36.8
55–59	10 433	5 162	5 271	12 006.8	115.1	113.0–117.2	7 460.2	144.5	141.3–147.8	4 492.8	85.2	82.8–87.8
60–64	8 473	4 130	4 343	16 036.9	189.3	186.2–192.1	9 173.5	222.1	217.6–226.7	6 740.3	155.2	151.5–158.9
18–64	79 350	39 865	39 484	37 753.5	47.6	47.1–48.1	23 056.9	57.8	57.1–58.6	14 509.8	36.7	36.2–37.4
45–64	34 690	17 189	17 501	34 302.2	98.9	97.8–99.9	20 674.7	120.3	118.7–121.9	13 436.5	76.8	75.5–78.1

[†]Estimated number of patients. [‡]95%CI: based on standard normal distribution. CI, confidence interval.

tions might be that cerebrovascular disease as an underlying illness of VaD is a common disease in middle age, so patients usually get medical treatment in general hospitals in Japan. On the other hand, early onset AD and DLB are still difficult to diagnose, so patients are referred from general hospitals or clinics to university hospitals for detailed examination.

The prevalence of FTLD in this study was lower than that in the UK (15.4%)[15,16] and the Netherlands (15.1%).[17] One possible reason is the rarity of familial FTLD cases in Japan, but otherwise the cause of this finding remains unknown.[21]

A limitation of the current study is that we could not confirm the accuracy of the diagnosis by neuropathological examination. Thus it remains possible that pathological diagnoses might alter the distribution due to mixed pathologies,[22] and vascular lesions might co-exist with other pathologies reducing the

Table 4. Comparison of prevalence of dementia per 100 000 in the 30–64-year-old age group among studies

Authors	Year	Country	Place	Age range	Population at risk	n	Prevalence	Target
Mölsä *et al.*[12]	1982	Finland	Turku	45–54	–	10	51.0	All dementia
				55–64		24	144.0	–
Kokmen *et al.*[13]	1989	USA	Rochester	45–49	–	2	77.0	All dementia
				50–54	–	1	40.0	–
				55–59	–	2	86.0	–
				60–64	–	5	249.0	–
Newens *et al.*[14]	1993	UK	Northern Health Region	45–64	655 800	227	34.6	AD
Ohshiro *et al.*[4]	1994	Japan	Tottori	40–64	209 621	100	81.4	All dementia
Ichinowatari *et al.*[5]	1997	Japan	5 catchment areas	18–64	3 729 706	1203	48.1	All dementia
Ratnavalli *et al.*[15]	2002	UK	London	45–64	326 019	59	81.0	All dementia
Harvey *et al.*[16]	2003	UK	–	30–64	240 766	130	54.0	All dementia
Rosso *et al.*[17]	2003	Netherlands	Zuid-Holland	30–59	1 435 769	21	1.5	FTLD
Present study	2009	Japan	5 catchment areas	18–64	9 370 651	2059	47.6	All dementia

AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; VaD, vascular dementia.

overall significance of vascular disease as a sole cause of the cognitive impairment. In addition, although EOD is likely to come to medical attention, it is possible that a certain proportion of individuals with EOD might not have been detected. For the purpose of reducing such referral bias, case ascertainment was thoroughly made by surveying both medical institutions and non-medical (LTCI) facilities. As a result, the present study attained very high response rates.

Finally, in Japan the government and media have become aware of the issues of EOD, but policies for EOD have not yet been established and support systems for early onset dementia are inadequate. We hope this study may provide, not only for Japan but also policy-makers in other countries, basic data to estimate budgets for evaluating and enabling an optimal EOD health-care policy.

ACKNOWLEDGMENTS

This study was supported in part by a research grant from the Japanese Ministry of Health, Labor and Welfare. We thank all the institutions for their assistance with medical record abstraction; David Darby for helpful comments; Hiroko Asada and Chieko Kobayashi for secretarial assistance; and Brian K. Purdue for native-speaker revision. There is no conflict of interest.

REFERENCES

1. Sampson E, Warren J, Rossor M. Young onset dementia. *Postgrad. Med. J.* 2004; **80**: 125–139.
2. Yokota O, Sasaki K, Fujisawa Y *et al.* Frequency of early and late-onset dementias in a Japanese memory disorders clinic. *Eur. J. Neurol.* 2005; **12**: 782–790.
3. Shinagawa S, Ikeda M, Toyota Y *et al.* Frequency and clinical characteristics of early-onset dementia in consecutive patients in a memory clinic. *Dement. Geriatr. Cogn. Disord.* 2007; **24**: 42–47.
4. Ohshiro H, Kurozawa Y, Iwai N, Nose T. Estimated prevalence of presenile dementia in Tottori Prefecture. *Nippon Koushuu Eisei Zasshi* 1994; **41**: 424–427 (in Japanese).
5. Ichinowatari N, Ootsuka T, Nagai M. *A Survey Report on the Revelation of Early-Onset Dementia*. The Ministry of Health, Labor, and Welfare, Tokyo, 1997; (in Japanese).
6. Ikejima C, Yasuno F, Mizukami K *et al.* Prevalence and causes of early-onset dementia in Japan: A population-based study. *Stroke* 2009; **40**: 2709–2714.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. American Psychiatric Association, Washington, DC, 1987.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington, DC, 1993.
9. Román GC, Tatemichi TK, Erkinjuntti T *et al.* Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; **43**: 250–260.
10. McKeith IG, Galasko D, Kosaka K *et al.* Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996; **47**: 1113–1124.
11. Neary D, Snowden JS, Gustafson L *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998; **51**: 1546–1554.
12. Mölsä PK, Mattila RJ, Rinne UK. Epidemiology of dementia in a Finnish population. *Acta Neurol. Scand.* 1982; **65**: 541–552.
13. Kokmen E, Beard CM, Offord KP, Kurland LT. Prevalence of medically diagnosed dementia in a defined United States population: Rochester, Minnesota, January 1 1975. *Neurology* 1989; **39**: 773–776.
14. Newens AJ, Forster DP, Kay DW, Kirkup W, Bates D, Edwardson J. Clinically diagnosed presenile dementia of the Alzheimer type in the Northern Health Region: ascertainment, prevalence, incidence and survival. *Psychol. Med.* 1993; **23**: 631–644.
15. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 2002; **58**: 1615–1621.
16. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J. Neurol. Neurosurg. Psychiatry* 2003; **74**: 1206–1209.
17. Rosso SM, Kaat LD, Baks T *et al.* Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. *Brain* 2003; **126**: 2016–2022.
18. Minematsu K, Yasaka M, Yonehara T *et al.* Multicenter survey of the diagnosis and management of stroke in young adults: Strategies against Stroke Study for Young Adults in Japan (SASSY-Japan). *Jpn. J. Stroke* 2004; **26**: 331–339 (in Japanese).
19. Reeves MJ, Bushnell CD, Howard G *et al.* Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* 2008; **7**: 915–926.
20. Ikeda M, Hokoishi K, Maki N *et al.* Increased prevalence of vascular dementia in Japan. *Neurology* 2001; **57**: 839–844.
21. Ikeda K. Neuropathological discrepancy between Japanese Pick's disease without Pick bodies and frontal lobe degeneration type of frontotemporal dementia proposed by Lund and Manchester Group. *Neuropathology* 2001; **20**: 76–82.
22. Jellinger KA, Attems J. Is there pure vascular dementia in old age. *J. Neurol. Sci.* 2010; **299**: 150–154.

International Psychogeriatrics: page 1 of 5 © International Psychogeriatric Association 2014
doi:10.1017/S1041610214000635

Family history of frontotemporal lobar degeneration in Asia – an international multi-center research

Ryuji Fukuhara,[1] Amitabha Ghosh,[2] Jong-Ling Fuh,[3,4] Jacqueline Dominguez,[5] Paulus Anam Ong,[6] Aparna Dutt,[2] Yi-Chien Liu,[7] Hibiki Tanaka[1] and Manabu Ikeda[1]

[1] *Department of Neuropsychiatry, Faculty of Life Science, Kumamoto University, 1-1-1, Honjo, Chuo-ku, Kumamoto-city, Japan*
[2] *Department of Neurology and Cognitive Neurology Unit, Apollo Gleneagles Hospitals, No. 58, Canal Circular Road, Kolkata 700 054, West Bengal, India*
[3] *Department of Neurology, Taipei Veterans General Hospital, No. 201, Sec. 2, Shipai Road, Beitou District, Taipei City, Taiwan*
[4] *National Yang-Ming University – School of Medicine, No. 155, Sec. 2, Linong Street, Taipei, Taiwan*
[5] *St. Lukes Medical Center, 279 E. Rodrtiguez Sr. Boulevard, Quezon City, Metro Manila, Philippines*
[6] *Department of Neurology, Hasan Sadikin Hospital, Faculty of Medicine, Padjadjaran University, Bandung, West Java, Indonesia*
[7] *Neurological Center, Cardinal Tien Hospital, No. 362, Zhongzheng Road, Xindian District, New Taipei City, 231, Taiwan*

ABSTRACT

Background: Previous studies in western countries have shown that about 30%–50% of patients with frontotemporal lobar degeneration (FTLD) have a positive family history, whereas the few epidemiological studies on FTLD done in Asia reported much lower frequencies. It is not clear the reason why the frequencies of FTLD with positive family history were lower in Asia. Furthermore, these findings were not from studies focused on family history. Therefore, it is necessary to conduct further studies on the family history of FTLD in Asia. This international multi-center research aims to investigate the family histories in patients with FTLD and related neurodegenerative diseases such as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and motor neuron diseases in a larger Asian cohort.

Methods: Participants were collected from five countries: India, Indonesia, Japan, Taiwan, and Philippines. All patients were diagnosed with behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), progressive non-fluent aphasia (PA), frontotemporal dementia with motor neuron disease (FTD/MND), PSP, and corticobasal degeneration (CBD) according to international consensus criteria. Family histories of FTLD and related neurodegenerative diseases were investigated in each patient.

Results: Ninety-one patients were included in this study. Forty-two patients were diagnosed to have bvFTD, two patients had FTD/MND, 22 had SD, 15 had PA, one had PA/CBS, five had CBS and four patients had PSP. Family history of any FTLD spectrum disorder was reported in 9.5% in bvFTD patients but in none of the SD or PA.

Conclusion: In contrast to patients of the western countries, few Asian FTLD patients have positive family histories of dementia.

Key words: Asia, epidemiology, family history, bvFTD, FTLD

Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common cause of early-onset dementia after Alzheimer's disease (AD; Neary, 1999). FTLD includes three clinical subtypes: frontotemporal dementia (bvFTD or behavioral variant FTD) characterized by a progressive deterioration of behavior and personality, as well as semantic dementia (SD) and progressive non-fluent aphasia variants of progressive aphasia (PA; Neary *et al.*, 1998). The broader FTLD spectrum also includes FTD with motor neuron disease (FTD/MND) and parkinsonian syndromes such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). While CBD requires a pathological diagnosis, the purely clinical entity is termed corticobasal syndrome (CBS).

Researches in western countries frequently report a strong family history in FTLD patients. In a community-based study by the Cambridge group, almost one-third of the participants (29%) with

Correspondence should be addressed to: Professor Manabu Ikeda, MD, PhD, Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University Hospital, 1-1-1, Honjo, Chuo-ku, Kumamoto-city 860-8556, Japan. Phone: +81-96-373-5566; Fax: +81-96-373-5566. Email: mikeda@kumamoto-u.ac.jp. Received 19 Oct 2013; revision requested 1 Dec 2013; revised version received 9 Mar 2014; accepted 16 Mar 2014.

FTLD had a positive family history (Ratnavalli *et al.*, 2002). In a nationwide survey in the Netherlands, 38% of FTLD patients had one or more first-degree relatives with dementia before the age of 80 years, compared with 15% of the control participants (Stevens *et al.*, 1998). In a hospital-based study by the Manchester group (Snowden *et al.*, 1996), a family history was seen in all subtypes of FTLD and 50 % of their bvFTD cases had a positive family history, similar to the findings in a Swedish series (Gustafson, 1987). On the other hand, there are only few studies on heredity in Asian FTLD patients. In the two clinic-based studies from Japan, family history was either absent (Ikeda *et al.*, 2004) or reported in less than 5% of FTLD patients (Wada-Isoe *et al.*, 2012). In a study from India, only 8.3% of bvFTD patients had a first-degree relative affected with a FTLD spectrum disorder (Ghosh *et al.*, 2013). The authors of the study also suggested that there could be distinctive behavioral patterns in Asian patients with bvFTD. Most patients in that study showed florid behavioral symptoms even in the early stages.

As advances in genetics and molecular pathology usher in clinical trials with biologically driven, disease-specific therapies for individual FTLD subtypes, it becomes essential to ensure that cross-cultural clinical and genetic differences in FTLD and its related disorders are clearly recognized. With this in mind, the present study aims to look at the family history in the different FTLD spectrum disorders in Asian countries.

Methods

Patients were recruited for the study from consecutive outpatients who attended the following Asian centers between January 2010 and December 2012: (1) Cognitive Neurology Unit, Department of Neurology, Apollo Gleneagles Hospitals (India), (2) Hasan Sadikin Hospital, Faculty of Medicine, Padjadjaran University (Indonesia), (3) Department of Neuropsychiatry, Faculty of Life Science, Kumamoto University Hospital (Japan), (4) St. Lukes Medical Center (Philippines), and (5) Taipei Veterans General Hospital and Cardinal Tien Hospital (Taiwan). All patients were examined by senior neurologists or psychiatrists and were assessed by a combination of careful medical history, laboratory testing, morphological imaging of brain such as magnetic resonance imaging (MRI) or computed tomography (CT), and functional imaging such as single photon emission computed tomography (SPECT), whenever possible. In some patients with severe behavioral symptoms, it was difficult to perform functional imaging without sedation. Patients were diagnosed with FTLD (bvFTD, SD, PA), FTD/MND, PSP, and CBS according to recognized diagnostic criteria (Brooks, 1994; Litvan *et al.*, 1996; Neary *et al.*, 1998; Boeve *et al.*, 2003). The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann *et al.*, 1984) were used to diagnose Alzheimer's disease. Only those patients who had reliable informants such as their spouses, were included in this study.

Each pedigree was investigated across five generations (first- and second-degree relatives) for any affected family member. Data obtained from interviewing patients and family members were used to make detailed family trees. The affected family members were categorized according to appropriate diagnostic criteria into one of the following disorders: bvFTD, SD, PA, FTD/MND, PSP, CBS, MND, Parkinson's disease, and other dementias. Age at onset and a medical history, whenever possible, were also obtained. When a family had more than one affected member, only a single proband was included to avoid overestimation.

All procedures followed the Clinical Study Guidelines of Ethics Committee of Kumamoto University Hospital, Apollo Gleneagles Hospitals, Taipei Veterans General Hospital, National Yang-Ming University Hospital, Hasan Sadikin Hospital, St. Lukes Medical Center, and Cardinal Tien Hospital, and were approved by the respective internal review boards. A complete description of the study procedures was provided to the patients and their caregivers and written informed consent was obtained from them.

Results

Ninety-one patients were recruited from the five institutes. Demographic data are shown in Table 1. Forty-two patients had a diagnosis of bvFTD, two patients had FTD/MND, 22 had SD, 15 had PA, one had PA/CBS, five had CBS, and four patients had PSP. One of the patients was clinically diagnosed as FTD/MND, who showed FTLD-TDP pathology by brain biopsy. This patient and two others were found to have the C9ORF72 mutation by genetic testing. The Mini-Mental State Examination (MMSE) scores, Clinical Dementia Rating (CDR) scores, average age at onset, and duration of illness at presentation are summarized in Table 2. The MMSE scores were not available in 13 patients because of their severe behavioral and/or language disturbances, while in four patients

Table 1. Demographic data for the 91 patients with frontotemporal lobar degeneration spectrum disorders

					NUMBER OF THE EACH DIAGNOSTIC GROUP						
	N	M/F	MEAN AGE AT ONSET (YEARS)	MEAN DURATION (YEARS)	BVFTD	FTD/MND	SD	PA	PA/CBS	CBS	PSP
India	39	29/10	61.4	3.2	23 (15)	1 (1)	5 (4)	3 (2)	0	4 (4)	3 (3)
Indonesia	4	0/4	55.0	5.5	3 (0)	0	0	0	1 (0)	0	0
Japan	18	11/7	62.5	5.7	5 (4)	0	9 (5)	2 (2)	0	1 (0)	1 (0)
Philippines	7	1/6	57.7	3.1	5 (1)	0	0	2 (0)	0	0	0
Taiwan	23	8/15	63.2	2.7	6 (2)	1 (0)	8 (2)	8 (4)	0	0	0
Total	91	49/42	61.5	3.7	42(22)	2 (1)	22 (11)	15 (8)	1 (0)	5 (4)	4(3)

Notes: The numbers within brackets denote the number of male patients.
bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

Table 2. Age, duration, MMSE scores, and CDR scores by diagnostic group

DIAGNOSIS OF PATIENTS	N	MEAN AGE AT ONSET (YEARS)	MEAN DURATION (YEARS)	MMSE SCORE	DISTRIBUTION OF CDR SCORE (0/0.5/1/2/3) (NUMBERS OF PATIENTS)
bvFTD	42	59.9	3.7	15.4	0/5/14/18/5*
FTD/MND	2	63.5	4.5	21.0	0/1/1/0/0
SD	22	59.5	1.8	14.3	0/4/12/1/3
PA	15	67.1	3.3	15.5	1/4/4/3/2
PA/CBS	1	76.0	5.0	–	0/0/0/1/0
CBS	5	64.0	1.7	18.2	0/1/2/2/0
PSP	4	61.3	3.3	21.5	0/1/2/0/0
Total	91	61.5	3.7	15.7	1/16/35/25/10

Notes: Numeral shows the number of patients in each CDR score.
Data of 13 cases in MMSE and 4 cases in CDR were could not available.
MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

CDR scores were not recorded. Sixty-six patients had information of all of their first-degree relatives. They include 35 patients with bvFTD, 14 with SD, seven with PA, one with PA/CBS overlap syndrome, five with CBS and four with PSP. Data on family history in the different FTLD spectrum disorders are shown in Table 3. Family history of any FTLD spectrum disorder was found in 5.5% of all patients, 9.5% of those with bvFTD, 50% of those with FTD/MND (out of only two patients), but in none of those with SD, PA, PA/CBS, CBS, and PSP. Among the four probands with bvFTD and positive family history, two also had family history of bvFTD, one had family history of PA, and one had family history of MND.

One bvFTD proband had three family members with FTD, including first-degree relatives, although neither pathological nor genetic data were available for any of them. Each of the other probands with bvFTD had only one other family member with a FTLD spectrum disorder. One of two probands with FTD/MND had one family member with MND. Family history of other dementias including AD and undiagnosed dementias was found in 27.5% of all patients, 26.2% of bvFTD, 27.3% of SD, 50% of PA, 75% of PSP, and in the only patient with PA/CBS overlap, but in none with FTD/MND or CBS.

Discussion

To date, family history in FTLD, reported mostly from western European and North American populations, has been seen in up to 40% of patients, with roughly 10% of patients showing an autosomal dominant inheritance pattern (Goldman *et al.*, 2005; 2007; van Swieten and Rosso, 2008). Relevant data from Asia are sparse (Ikeda *et al.*, 2004; Ghosh *et al.*, 2013). Our study is one of the

Table 3. Family history data in each diagnostic group

		FAMILY MEMBERS AFFECTED WITH FTLD AND RELATED DISEASES		FAMILY MEMBERS AFFECTED WITH OTHER OR UNDIAGNOSED DEMENTIA	
DIAGNOSIS OF PATIENTS	N	N	%	N	%
bvFTD	42	4 (including 1 MND)	9.5	11	26.2
FTD/MND	2	1 (MND)	50.0	0	0.0
SD	22	0	0.0	6	27.3
PA	15	0	0.0	4	26.7
PA/CBS	1	0	0.0	1	100.0
CBS	5	0	0.0	0	0.0
PSP	4	0	0.0	3	75.0
Total	91	5	5.5	25	27.5

Notes: FTLD and related diseases included FTLD spectrum disorders and MND. One patient with MND among four affecting family members in bvFTD group: one affected family member with MND in the FTD/MND group.
bvFTD = behavioural variant frontotemporal dementia; FTD/MND = frontotemporal dementia with motor neuron disease; SD = semantic dementia; PA = progressive non-fluent aphasia; PA/CBS = progressive non-fluent dementia and corticobasal syndrome overlap; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy.

largest reports of FTLD in an Asian population. A positive family history of FTLD spectrum disorders was found in 5.5% of our patients. Together with the previous Asian studies, our findings, therefore, support the infrequent occurrence of family history in Asian FTLD patients. It might be due to genetic differences between western and Asian populations.

In our patients, only one proband with bvFTD showed a clear autosomal dominant inheritance pattern, whereas none of the SD patients gave a family history of any FTLD spectrum disorder. Goldman *et al.* (2005) reported autosomal dominant inheritance in 18.2% of their patients with bvFTD and 1.9% of their SD patients, while Rohrer *et al.* (2009) described this inheritance pattern in 20% of their bvFTD patients but not in their SD patients. Goldman *et al.* (2005) also showed that familial aggregation, in which there were three or more affected family members, occurred in 8.1% of bvFTD patients but not in SD patients, and that 18.2% of bvFTD patients and 15.1% of SD patients had a single affected first-degree relative. In our study, most of the bvFTD patients had sporadic disease and only 2.4% of patients had a single affected relative. Therefore, in Asia, the occurrence of familial FTLD is undoubtedly lower than that in the western countries.

In recent years, various genetic abnormalities in microtubule-associated protein tau (MAPT), progranulin (GRN), and C9ORF72 have been associated with familial FTLD. In Asia, MAPT mutations have been reported in familial SD (Ishizuka *et al.*, 2011), although typically in low frequency (Wada-Isoe *et al.*, 2012). These results suggest that genetic factors for the development of FTLD may have a less important role in the Asian population. Rohrer *et al.* (2009) demonstrated that 186 out of the 225 FTLD patients in their study had no mutations in known genes such as MAPT, GRN, valosin-containing protein (VCP), TARDP, chromatin modifying protein 2B (CHMP2B), and fused in sarcoma (FUS), and did not show strong family history. Unknown genetic defects may be associated with the development of many sporadic FTLD cases.

There are several limitations in the current study. First, although diagnosis of each proband was based on comprehensive examination including brain imaging, and followed recognized consensus criteria, the information regarding family histories were obtained by semi-structured interviews of the proband and family members. It was thereby difficult to confirm the diagnosis in many deceased or distant family members. Second, for most of our patients the diagnosis was based on clinical criteria and was not confirmed by definite pathological or genetic tests. However, going by the number of patients with FTLD spectrum disorders recruited for this study, this may be the largest research to date focusing on the family history of these disorders in Asia. This could, therefore, form the basis for future neurogenetic research in Asian countries.

Conclusion

Previous epidemiological studies have suggested that familial FTLD was rare in Asian countries. The current study, by focusing on family history in FTLD patients, demonstrated that, unlike patients from western countries, few Asian FTLD patients have a positive family history of dementia. Future research could explore possible reasons underlying these differences.

Conflict of interest

None.

Description of author's roles

R. Fukuhara participated in the study design, analyzed the data, and wrote the paper. A. Ghosh, J. Fuh, J. Dominguez, and P. A. Ong carried out clinical assessment, collected the data, and edited and revised the paper. A. Dutt and Y. Liu carried out clinical assessment and collected data. H. Tanaka carried out clinical assessment, collected the data, and assisted the analyses. M. Ikeda participated in the study design, and editing and revising the paper. All of the authors contributed to and approved the manuscript.

Acknowledgments

This research was administered as a part of the scientific research conducted by the Ministry of Education, Culture, Sports, Science and Technology of Japan for M.I. (Grant No. 23591718).

References

Boeve, B. F., Lang, A. E. and Litvan, I. (2003). Corticobasal degeneration and its relationship to progressive supranuclear palsy and fronto-temporal dementia. *Annals of Neurology*, 54 (Suppl. 5), S15–S19.

Brooks, B. R. (1994). El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on motor neuron diseases/amyotrophic lateral sclerosis of the World Federation of Neurology Research Group on neuromuscular diseases and the El Escorial "Clinical Limits of Amyotrophic Lateral Sclerosis" workshop contributors. *Journal of the Neurological Sciences*, 124, 96–107.

Ghosh, A., Dutt, A., Ghosh, M., Bhargava, P. and Rao, S. (2013). Using the revised diagnostic criteria for frontotemporal dementia in India: evidence of an advanced and florid disease. *PLoS ONE*, 8, e60999.

Goldman, J. S. *et al.* (2005). Comparison of family histories in FTLD subtypes and related tauopathies. *Neurology*, 65, 1817–1819.

Goldman, J. S., Adamson, J., Karydas, A., Miller, B. L. and Hutton, M. (2007). New genes, new dilemmas: FTLD genetics and its implications for families. *American Journal of Alzheimer's Disease and Other Dementias*, 22, 507–515.

Gustafson, L. (1987). Frontal lobe degeneration of non-Alzheimer type. II. Clinical picture and differential diagnosis. *Archives of Gerontology and Geriatrics*, 6, 209–223.

Ikeda, M., Ishikawa, T. and Tanabe, H. (2004). Epidemiology of frontotemporal lobar degeneration. *Dementia and Geriatric Cognitive Disorders*, 17, 265–268.

Ishizuka, T., Nakamura, M., Ichiba, M. and Sano, A. (2011). Familial semantic dementia with P301L mutation in the Tau gene. *Dementia and Geriatric Cognitive Disorders*, 31, 334–340.

Litvan, I. *et al.* (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*, 47, 1–9.

McKhann, G. *et al.* (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34, 939–944.

Neary, D. (1999). Overview of frontotemporal dementias and the consensus applied. *Dementia and Geriatric Cognitive Disorders*, 10 (Suppl. 1), 6–9.

Neary, D. *et al.* (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, 51, 1546–1554.

Rohrer, J. D. *et al.* (2009). The heritability and genetics of frontotemporal lobar degeneration. *Neurology*, 73, 1451–1456.

Snowden, J. S., Neary, D. and Mann, D. M. A. (1996). *Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia*. New York, NY: Churchill Livingstone.

Ratnavalli, E., Brayne, C., Dawson, K. and Hodges, J. R. (2002). The prevalence of frontotemporal dementia. *Neurology*, 58, 1615–1621.

Stevens, M. *et al.* (1998). Familial aggregation in frontotemporal dementia. *Neurology*, 50, 1541–1545.

van Swieten, J. C. and Rosso, S. M. (2008). Epidemiological aspects of frontotemporal dementia. *Handbook of Clinical Neurology*, 89, 331–341.

Wada-Isoe, K. *et al.* (2012). Epidemiological survey of frontotemporal lobar degeneration in tottori prefecture, Japan. *Dementia and Geriatric Cognitive Disorders EXTRA*, 2, 381–386.

Journal of Affective Disorders 162 (2014) 30–33

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

Item non-response on self-reported depression screening questionnaire among community-dwelling elderly

Asuka Koyama [a,*], Ryuta Fukunaga [b], Yasuhisa Abe [b], Yoshitomo Nishi [a], Noboru Fujise [a], Manabu Ikeda [a]

[a] Department of Neuropsychiatry, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto, Japan
[b] Yatsushiro Kousei Hospital, Kumamoto, Japan

ARTICLE INFO

Article history:
Received 10 March 2014
Accepted 14 March 2014
Available online 27 March 2014

Keywords:
Complete case analysis
GDS
Japan

ABSTRACT

Background: In responses to self-reported depression screening questionnaires, item non-response, which refers to the absence of answers to specific questions, is problematic. The objective of this study were (1) to clarify the features of respondents with item non-response on a self-reported elderly depression screening questionnaire (15-item geriatric depression scale; GDS-15) as compared to respondents with full responses, and (2) to compare positive depression screening rates calculated using two methods: excluding respondents with item non-response (complete case analysis; CCA) and estimating by multiplying mean scores from valid responses by the total number of GDS-15 items for respondents with item non-response.

Methods: This was a cross-sectional study conducted from 2010 to 2012. Of 4794 elderly subjects (65 years and older) living in one town in Japan 2836 community-dwelling elderly people (59.2%) were included in the analysis.

Results: Item non-response was observed in 25.0% of respondents. Respondents with item non-response had a higher rate of depression and mental and physical problems. Respondents with depression (estimated GDS-15 score ≥ 6) and suicidal ideation both had a 1.6-times higher risk of item non-response on the GDS-15. The positive depression screening rate on GDS-15 by CCA was 16.5%, compared with 18.9% when calculated by the estimated GDS-15 score.

Limitations: Our survey was conducted in one rural area and targeted only elderly people.

Conclusion: The incidence of item non-response among community-dwelling elderly people was associated with depression of the respondent. Excluding subjects with item non-response when calculating positive depression screening rates in elderly individuals causes the rate to be underestimated.

1. Introduction

Although self-reported survey research is convenient, inexpensive, and places little burden on respondents, item non-response, that is, absence of answers to specific questions, is problematic (Yan and Curtin, 2010). Item non-response occurs for many reasons, including careless mistakes, refusal to respond to questions about private issues, the absence of a "not applicable" option, or use of questions that the respondent does not understand.

The complete case analysis (CCA) method is commonly used to address missing data from survey respondents by excluding subjects with missing data from analysis. If item non-response occurs at random (referred to as "Missing Completely at Random"), it can be ignored. CCA is convenient for this type of data, although it decreases the number of respondents. However, other types of missing data may also occur. These include "Missing at Random" data, in which the incidence of missing responses depends on some measurable characteristic of the individual but not on the missing value itself, and "Missing not at Random" data, in which the incidence of missing depends on missing itself. For example, people with high or low income might be less likely to report their income. For both "Missing at Random" and "Missing not at Random" data, missing itself has an important meaning and the results determined by complete case analysis are biased.

We had an opportunity to analyze secondary data of depression among community-dwelling elderly assessed by the geriatric depression scale (GDS)-15 Japanese version, a self-reported questionnaire (Niino et al., 1991). We hypothesized that item non-response would

* Corresponding author.
E-mail addresses: asuka@fc.kuh.kumamoto-u.ac.jp (A. Koyama), rtfkng@gmail.com (R. Fukunaga), abeb42@gmail.com (Y. Abe), yoshitomo.nishi@nifty.com (Y. Nishi), nfujise@kumamoto-u.ac.jp (N. Fujise), mikeda@kumamoto-u.ac.jp (M. Ikeda).

http://dx.doi.org/10.1016/j.jad.2014.03.022
0165-0327/

not occur at random because depression itself affects the incidence of item non-response. For example, depressed people often lack motivation and have difficulty concentrating, which may lead to missing responses. In addition, item non-response may occur in elderly respondents due to decreases in cognitive function. However, little is known about the issue of item non-response on a self-reported elderly depression screening questionnaire. Although Shrive et al. described how to deal with missing data on the Zung Self-reported Depression scale using six different imputation techniques, they carried out random simulations using only the full-response group (Shrive et al., 2006), which does not reflect a real non-response situation.

The aim of this study is to clarify features of respondents with item non-response on the GDS-15 compared with respondents with full-responses and compare positive depression screening rates calculated using CCA with rates determined by GDS-15 estimated by multiplying mean scores from valid responses by the number of total GDS-15 items. Our hypothesis is that rates calculated using CCA will underestimate the true rate of depression.

2. Methods

2.1. Participants and procedures

We used secondary data obtained from an epidemiologic survey study conducted from 2010 to 2012 in Asagiri, Kumamoto, Japan. Asagiri has suffered from depopulation and aging. A detailed description of the survey is available elsewhere (Fukunaga et al., 2012).

In each year, one area of the town was selected and all residents aged 65 years and older received a self-reported questionnaire by postal mail. They were asked to return questionnaires using the return envelope. Returning the questionnaire was assumed to represent informed consent. Of 4794 subjects, 3167 (66.1%) returned the questionnaire. A total of 331 subjects who were in the hospital or nursing home or who could not answer because of dementia or other reasons were excluded. All procedures for the present study followed the 2009 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital (Kumamoto, Japan) and were approved by the Internal Review Board.

2.2. Measures

GDS was used to assess depression. Although a standard 30-item version (Yesavage et al., 1983) and a shortened 15-item version (Sheikh and Yesavage, 1986) are available, this study used the Japanese 15-item version. GDS-15 Japanese version has a sufficient reliability and validity (Watanabe and Imagawa, 2013). For each item, subjects answered "Yes" or "No". Depressive answers were scored 1-point for each item and sum of all items represented the GDS-15 total score (range, 0–15). A score of 6 or more is considered to represent 'possible depression' (Schreiner et al., 2001).

Other variables assessed included age, gender, living alone or not, routine hospital visits, sleep problems (having/not having), appetite (having/not having), serious worries about money (having/not having), suicidal ideation (having [included "sometimes", "often", and "always"]/not having).

2.3. Statistical analysis

For statistical analysis, we calculated the incidence of item non-response on the GDS-15 by counting the number of unanswered items. Respondents who failed to answer one or more questions were defined as the "item non-response group" and those who answered all questions were defined as the "full-response group." We compared sociodemographic characteristics, physical and mental complaints, and each item of the GDS-15 between the item non-response group and full-response group, excluding cases with item non-response in each analysis. Second, we compared mean GDS-15 scores and the percentage of respondents who scored ≥ 6 between two groups. For item non-response group, we estimated GDS-15 scores by multiplying the mean score from valid responses by the number of GDS-15 items. Logistic regression analysis was conducted to assess the likelihood of item non-response among depressive respondents or respondents with suicidal ideation. In addition, we compared the positive screening rate calculated by CCA with the one determined by GDS-15 estimates (multiplying the mean score from valid responses by the number of GDS-15 all items). All tests were 2-tailed and the significance levels were Bonferroni-corrected. All statistical analyses were performed with SPSS 21.0J for Windows (IBM SPSS Japan, Tokyo, Japan).

3. Results

Of 2836 subjects, 719 (25.0%) were included in the "item non-response group". In this group, 54% did not respond to 1 item, 19% did not respond to 2 items, 15% did not respond to 3 to 5 items, 9% did not respond to 6 to 14 items, and 4% did not respond to any item. Mean age and the percentage of females were significantly higher in the item non-response group than the full-response group. In the item non-response group, the percentage with routine hospital visits, sleep problems, loss of appetite, and having suicidal ideation was significantly higher than in the full-response group. The GDS-15 mean score and the percentage of the respondents who scored cutoff point of 6 or more of GDS-15 were significantly higher in the item non-response group than in the full-response group (Table 1).

Table 2 shows the incidence of item non-response of all respondents for each GDS-15 item and the comparison of the percentage of depressive answers in each item between groups. In 13 of 15 items, the percentage of respondents who selected depressive answers was significantly higher in the item non-response group than in the full-response group.

Logistic regression analysis revealed that the existence of depression (GDS-15 score ≥ 6) and suicidal ideation were risk factors for item non-response after adjusting for age, gender, and routine hospital visits. Odds ratios were 1.6 (95% CI, 1.3–2.0, $p < 0.001$) and 1.6 (95% CI, 1.2–2.0, $p < 0.001$), respectively.

When we calculated the positive depression screening rate on GDS-15 by CCA, that is, excluding the item non-response group, the percentage was 16.5%. When we calculated GDS-15 score in item non-response group by mutiplying mean scores from valid responses by the number of total GDS-15 items, the total positive rate was 18.9%, which was remarkably higher than that calculated using CCA.

4. Discussion

The present study was the first to show a correlation between the incidence of item non-response and depression among elderly community-dwelling survey respondents. Respondents with depression and suicidal ideation had a 1.6 times higher risk of item non-response on the GDS-15. In addition, the rate calculated using CCA was lower than GDS-15 estimates determined by multiplying mean scores from valid responses by the number of total GDS-15 items. From these findings, we could conclude that the rate of depression calculated using CCA would be underestimated. Recently, imputation methods such as multiple imputation analysis have been gaining use when dealing with item non-response (Rubin, 1987). However, this technique has some restrictions. For

Table 1
Comparison of demographic and other characteristics between the item non-response and full-response groups.

	Item non-response group ($N=719$)	Full-response group ($N=2117$)	t/χ^{2c}
Mean age[a]	78.0	76.0	$t=6.8^{**}$
Gender [a] (female, %)	66.0	56.8	$\chi^2=18.3^{**}$
Living alone[a] (%)	14.9	12.0	$\chi^2=4.0$
Routine hospital visit[a] (having, %)	85.5	79.8	$\chi^2=10.7^{*}$
Seep problems[a] (having, %)	32.7	23.2	$\chi^2=24.6^{**}$
Loss of appetite[a] (having, %)	15.2	9.7	$\chi^2=16.0^{**}$
Worries about money[a] (having, %)	13.0	9.7	$\chi^2=6.0$
Suicidal ideation[a] (having, %)	19.8	11.6	$\chi^2=28.0^{**}$
Mean GDS-15 score[b]	4.1	2.8	$t=8.5^{**}$
Cutoff score ≥ 6[b] (%)	26.1	16.5	$\chi^2=31.7^{**}$

[a] Excluded respondents who did not respond to each factor.
[b] Excluded 26 respondents with full non-response.
[c] * < 0.05, ** < 0.01; Bonferroni-corrected.

Table 2
Incidence rate of item non-response and comparison of the percentage of depressive answers between the item non-response and full-response groups.

GDS-15 items	Incidence rate of item non-response (%)	The percentage of depressive answer		
		Item non-response group ($N=719$)	Full-response group ($N=2117$)	χ^{2a}
Are you basically satisfied with your life? YES/**NO**	2.6	15.3	12.1	4.7
Have you dropped many of your activities and interests? **YES**/NO	4.9	32.6	22.2	26.6**
Do you feel that your life is empty? **YES**/NO	4.1	19.0	11.0	23.5**
Do you often get bored? **YES**/NO	6.1	29.3	21.5	14.5**
Are you in good spirits most of the time? YES/**NO**	7.2	24.5	17.9	15.8**
Are you afraid that something bad is going to happen to you? **YES**/NO	3.9	16.9	11.1	14.6**
Do you feel happy most of the time? YES/**NO**	3.7	16.4	9.1	26.6**
Do you often feel helpless? **YES**/NO	7.9	27.5	21.9	7.1
Do you prefer to stay at home, rather than going out and doing new things? **YES**/NO	3.2	46.8	34.6	30.7**
Do you feel you have more problems with memory than most? **YES**/NO	3.6	41.4	27.5	43.7**
Do you think it is wonderful to be alive now? YES/**NO**	3.4	11.9	7.3	13.6*
Do you feel pretty worthless the way you are now? **YES**/NO	4.8	20.1	10.6	37.0**
Do you feel full of energy? YES/**NO**	4.0	50.3	36.3	39.0**
Do you feel that your situation is hopeless? **YES**/NO	5.1	12.0	7.1	14.3**
Do you think that most people are better off than you are? **YES**/NO	6.3	42.7	29.2	36.2**

Answers in bold indicate depressive answer. One point is scored for each bolded answer.
[a] * < 0.05, ** < 0.01; Bonferroni-corrected.

example, multiple imputation analysis cannot be used with "Missing not at Random" data or categorical data. Previous studies suggest that the most suitable way to deal with item non-response differs depending on the research topic (Desai et al., 2011; Ali et al., 2011; Hallgren and Witkiewitz, 2013; Ng et al., 2013). Thus, item non-response should be handled with extreme caution and results interpreted cautiously.

Elderly or depressive respondents are thought to have a higher risk of item non-response (Mody et al., 2008). Elderly people are more likely to miss or skip more items because of cognitive impairment including difficulty in understanding and judgment or physical problems such as vision deficits, whereas depressed patients tend to have low motivation, inability to concentrate, or easy fatigability. Thus, creating a questionnaire that is easy for every respondent to answer is also important (e.g., increasing the size of the text or changing the color for each line). This would be effective not only for elderly or depressive respondents but for all respondents.

Item non-response occurred more frequently in females than in males, which is consistent with a previous study (Ying, 1989). This finding may reflect the fact that female respondents are older than male respondents, as the average lifespan is longer for females than males in Japan and other countries.

4.1. Limitations

Our study has several limitations. First, it is difficult to generalize our results because our survey was conducted in one rural area and targeted only elderly people. Second, we could not distinguish writing from dictation from self-written responses in our survey. For cases of writing from dictation, the incidence of item non-response might be lower. In addition, the issue of "unit non-response" should be determined as well as item non-response. Unit non-response means that an eligible sample unit fails to participate in a survey because of failure to establish contact or refusal to cooperate. Some studies reported worse health status among the unit non-response group, although others reported opposite findings (Volken, 2013). Further studies about item and unit non-response among patients diagnosed with depression and the correlation between item non-response and severity of depression are needed to support our results.

4.2. Conclusions and clinical implications

Our study revealed that the incidence of item non-response among community-dwelling elderly people was associated with depression of the respondent. When calculating positive