Step 2

For the second step of the postal survey, respondent institutions with one or more cases were asked to provide additional patient data including: initials, demographics, coexisting illnesses, duration and type of dementia (in the case of vascular dementia, specifying the subtype of cerebrovascular disease), severity of dementia, and functional status. Patients were then classified into subgroups according to the cause of their dementia. Alzheimer Disease (AD), vascular dementia (VaD), and alcohol-related dementia were defined according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[6]. dementia with Lewy bodies and Parkinson Disease with dementia were diagnosed according to the revised criteria for the clinical diagnosis of dementia with Lewy bodies[7], and frontotemporal lobar degeneration was diagnosed according to Lund and Manchester Criteria.[8] Finally, patients fulfilling the DSM-III-R criteria for dementia, but not fulfilling criteria for any of the above diagnostic categories, were assigned to the "other" category.

Answers for the additional information for cases reported from non-medical institutions were made based on comments by the consulting physicians at these institutions . 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. During step 1 and 2, up to three reminder letters were sent to institutions that had failed to respond in order to maximize the size of the population.

Quality control

For quality control purposes, we selected the 9 institutions with the highest number of reported EOD cases from those that had responded. Each of these institutions reported 5 or more cases and specialized in medical practice for dementia or stroke. For about half of the reported patients identified at step 2, key psychiatrists and doctors of the selected institutions together reviewed their medical records and data, including the results of magnetic resonance imaging (MRI), computed tomography (CT), and single photon emission computed tomography (SPECT).

Statistical analysis

In order to reduce sampling bias due to failure to report cases, the prevalence was estimated for each institutional group adjusting for the reported response rates. For each category of institution: (i) the reciprocal of the product of the response rate for the first and

second steps (sample weight) was calculated, and (ii) the estimated number of patients in the category was calculated using the sample weight multiplied by the reported number of cases. The total number of patients across categories was then estimated by the sum of the estimated category totals." We calculated 95% confidence intervals (CI) based upon the Poisson distribution. The population denominators used were derived from Census data of the target area on April 1, 2006.[9] The significance of differences between rates was estimated by chi-square tests or Fisher's exact tests. All analyses were carried out using SAS software, version 9.1 (SAS Institute).

RESULTS

Table 1 shows the response rate for the postal surveys. In total, information from 717 patients was collected from 285 institutions.

After careful review of the answer sheets, reported patients with the following diagnoses were excluded: schizophrenia (n = 6), developmental disorder (n = 11), depression (n = 2), and other non-dementia disorders (n = 4). None of these patients were considered to have had concomitant EOD. In addition, 29 patients were excluded because their age on the Census day was over 65, although their age at onset of dementia was less than 65. In some instances, two or more institutions contributed reports on the same individual cases: 36 individuals

from two institutions; 2 individuals from three institutions; and one individual from four institutions. Five cases received different diagnoses: 4 with AD also classified as DLB, and 1 with AD also classified as alcohol-related dementia.

For the cases lacking diagnostic agreement, we accepted the final diagnosis of the most experienced clinical assessors according to the following order: diagnosis made by neurologists or psychiatrists of a general hospital including university hospitals; psychiatrists of psychiatric hospitals; physicians of general hospitals; physicians of clinics; and physicians from other health-care facilities. As a result, the final diagnosis for all of the former 4 cases was DLB and the latter case was AD. The final sample population was comprised of 617 patients (59.2% male). Of these, 286 patients received the study quality control evaluation (Figure 1). The mean age on Census day of this group was 56.9 years (SD, 7.3; range, 22-64 y) and the mean age at onset of dementia was 53.4 years (7.9; 18-64 y).

Of the illnesses causing EOD, vascular dementia (VaD) was the most frequent (42.5%), followed by Alzheimer Disease (AD) (25.6%), head trauma (7.1%), dementia with Lewy bodies (DLB)/Parkinson Disease with dementia (PDD)(6.2%), frontotemporal lobar degeneration (FTLD) (2.8%), and others (16.0%) (Figure 2). The frequency of the illnesses causing EOD was calculated

from two subgroups: Quality control detailed evaluation group (n=286); and Clinical records only group (n=331) (see fig.1). Subgroup analysis did not change the overall order of the three most frequent illnesses, namely VaD, AD, and DLB. However, there were significant differences in the frequencies for each illness ($p<0.0001$), with similar values for VaD (49.7%, 39.6%) and AD (25.1%, 31.3%) but higher frequencies for DLB (2.9%, 12.3%) and FTLD (1.2%, 5.3%) for the selected subgroup under the quality control condition.

Subtypes of VaD were cerebral hemorrhage (37.5%), large cortical infarct (34.1%), subarachnoid hemorrhage (20.1%), multiple lacunar infarct (2.3%), mixed cerebrovascular disease (e.g., cerebrovascular hemorrhage and large cortical infarct) (2.0%), other VaD (e.g., moyamoya disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) (2.0%), and unspecified VaD (2.7%) (Figure 2). The "other" category included dementia secondary to alcohol related dementia (2.8%), infection (2.3%), surgery for brain tumor (1.5%), and hypoxia (1.0%). The total estimated number of patients using the reciprocal of the response rate for both steps expected in the Prefecture was calculated to be 761. The prevalence rate in those aged 20 to 64 was 42.3 per 100,000 (95% CI, 39.4-45.4). From the age of 30 onwards, the prevalence rate of dementia approximately doubled with each 5-year increase in

age (Table 2).

Figure 3 shows the prevalence rate of AD and VaD by sex. The most frequent illness causing EOD was VaD in males and AD in females.

DISCUSSION

One of the key findings of the present study was the prominence of VaD as the most frequent underlying cause of EOD. Until recently, VaD had been considered to be the most frequent cause of late-onset dementia (LOD) in Japan. However, a series of recent reports showed in fact a higher proportion of AD than VaD among the elderly population.[10,11] Thus, the discrepancy in the causes of dementia between our EOD study and recent Japanese LOD studies requires explanation.

It is well known that aging is the most important risk factor for the development of AD, and in Japan the average life expectancy has been rising, with Japanese women now having the longest life expectancy in the world. The rise in life expectancy is likely to have contributed to the increase of AD. On the other hand, it has been said that the prevalence and incidence of stroke causing VaD has decreased in recent years. For example, the Hisayama study,[12] which is the longest duration longitudinal community-based stroke study in Japan, reported that the incidence of stroke had decreased in all age groups except the

pre-senile group. This finding indicates that VaD as an illness causing dementia has likely decreased in the elderly but not in the pre-senile population. Furthermore, increases in life expectancy would not be expected to affect the incidence of early onset AD. These observations could account in part for the discrepancy between causes of dementia in pre-senile and senile populations.

Another important issue is the difference in the pathogenesis of stroke between pre-senile and senile populations. The Japanese Standard Stroke Registry Study (JSSRS) used data from 16,630 stroke patients from many centers.[13] According to the JSSRS report, the peak age group for occurrence of subarachnoid hemorrhage is 50-59, for cerebral hemorrhage it is 60-79, and for lacunar infarction it is 70-79. This report indicated that cerebral and subarachnoid hemorrhage cause the majority of pre-senile strokes, while lacunar infarction is the main cause of senile stroke. It was also reported that amongst the various vascular illnesses causing VaD in the senile population, lacunar stroke had decreased in frequency, whilst no reduction in the proportion of cerebral and subarachnoid hemorrhage has yet been reported.[14] Hence, haemorrhages have been assumed to be the most common causes of pre-senile VaD. Our study appears to support this, with cerebral hemorrhage and subarachnoid hemorrhage accounting for 57.6% of conditions causing VaD.

There is also a discrepancy between the predominant causes of EOD in the current study and those reported previously in Western countries[15-17]. More than two decades ago, a Finnish study[18] study showed the incidence of stroke for Japanese pre-senile men as more than twice as high as that for the Caucasian pre-senile population of men and women combined. As described above, the incidence of stroke in the Japanese pre-senile group has probably not decreased. In addition, the results of the current study (Figure 4) show that the frequency of VaD for men was twice as high as for women, and this ratio is the same as that reported for all strokes in the Japanese general population for this age group.[19] Thus the prominence of VaD as an illness causing EOD appears to be attributable to the higher prevalence of stroke in pre-senile men.

Another key finding of this study is the higher frequency of DLB, which has recently been recognized as an illness and a common form of dementia in old age. Population-based studies investigating the prevalence of DLB are limited, particularly in younger populations.[20] The number of patients with DLB was the third highest in our study which is surprising considering the association of Parkinson's disease and advancing age. A limitation of the current study is that the accuracy of these diagnoses was not able to be confirmed by neuropathological examination. In addition, although EOD is likely to come to

medical attention, it remains possible that a proportion of individuals with EOD might not have been detected by the healthcare service.

To our knowledge, this is one of the largest studies estimating the prevalence of pre-senile dementia in a large community sample (Table 3). Case ascertainment was also more thorough including both medical institutions and non-medical (LTCI) facilities. In addition, the study attained very high institutional response rates increasing the likely accuracy of the inferences about population prevalence.

Finally, it is clear that there is a sizable number of individuals with EOD in Japan who require support both by their caregivers and access to public services. The needs of these patients who, in comparison with elderly individuals, are more likely to have dependents and financial commitments are an area urgently requiring further evaluation. . In addition, conventional services for individuals with dementia in Japan were designed for older people, which are likely to be sub-optimal or inappropriate for the needs of younger individuals with EOD. This study may provide policymakers with basic data to estimate the budgets for evaluating and enabling optimal EOD healthcare policy.

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Table 1. Response rates of the postal surveys

Institutions	step1			step2			
	Target populations	n*	Response rate (%)	Target populations	n	Response rate (%)	Reported cases
Hospitals (>200 beds)†	54	53	(98.1)	22	21	(95.5)	203
Hospitals (<200 beds)	113	106	(93.8)	21	16	(76.2)	186
Clinics	1,269	1111	(87.5)	46	37	(80.4)	53
Health service facilities	103	91	(88.3)	31	28	(90.3)	66
Special nursing homes	297	272	(91.6)	54	44	(81.5)	56
Group homes	242	198	(81.8)	45	41	(91.1)	52
Home-visit nursing facilities	100	93	(93.0)	19	18	(94.7)	31
Welfare living centers	156	145	(92.9)	25	22	(88.0)	29
Government services	69	66	(95.7)	9	8	(88.9)	23
Local welfare commissioners	47	46	(97.9)	10	8	(80.0)	17
Care managers	25	21	(84.0)	3	2	(66.7)	1
Total	2,475	2,202	(89.0)	285	245	(86.0)	717

*n: number of respondent institutions.

†Hospitals (>200beds) include University of Tsukuba.

Table 2. Age-specific prevalence per 100,000 for the causes of dementia in Ibaraki Prefecture, Japan, April 1, 2006

		All dementia				Vascular dementia				Alzheimer disease			
age range	population	n*	prevalence	95%CI†		n	prevalence	95% CI		n	prevalence	95% CI	
20-24	162,710	2	1.5	(0.5 -	4.9)	0	0.0	(0.0 -	2.4)	0	0.0	(0.0 -	2.4
25-30	184,565	7	4.0	(2.0 -	8.1)	0	0.0	(0.0 -	2.1)	0	0.0	(0.0 -	2.1
30-34	218,539	9	4.2	(2.3 -	8.0)	3	1.3	(0.4 -	3.9)	0	0.0	(0.0 -	1.8
35-39	199,124	10	4.9	(2.7 -	9.1)	7	3.5	(1.7 -	7.3)	1	0.7	(0.2 -	3.2
40-44	181,513	22	11.9	(7.8 -	18.1)	17	9.2	(5.7 -	14.8)	0	0.0	(0.0 -	2.1
45-49	186,253	45	24.3	(18.1 -	32.4)	20	10.7	(6.9 -	16.6)	1	0.8	(0.2 -	3.4
50-54	218,713	109	50.0	(41.5 -	60.3)	50	22.9	(17.4 -	30.2)	21	9.8	(6.4 -	14.9
55-59	254,615	240	94.3	(83.1 -	107.0)	107	42.2	(34.9 -	50.9)	71	28.0	(22.2 -	35.3
60-64	193,308	316	163.3	(146.3 -	182.4)	152	78.4	(66.9 -	92.0)	96	49.5	(40.6 -	60.5
20-64	1,799,340	761	42.3	(39.4 -	45.4)	356	19.8	(17.8 -	21.9)	191	10.6	(9.2 -	12.2
45-64	852,889	710	83.3	(77.4 -	89.6)	329	38.6	(34.6 -	43.0)	190	22.3	(19.3 -	25.7

*Estimated number of patients.
†95% confidence interval for the prevalence.

Table2 continued

age range	population	Head trauma			Frontotemporal lobar degeneration			Dementia with Lewy bodies/ Parkinson disease with dementia		
		n *	prevalence	95%CI †	n	prevalence	95% CI	n	prevalence	95% CI
20-24	162,710	2	1.5	(0.5 - 4.9)	0	0.0	(0.0 - 2.4)	0	0.0	(0 - 2.36)
25-30	184,565	7	4.0	(2.0 - 8.1)	0	0.0	(0.0 - 2.1)	0	0.0	(0 - 2.08)
30-34	218,539	2	1.1	(0.3 - 3.7)	1	0.6	(0.1 - 2.8)	0	0.0	(0 - 1.76)
35-39	199,124	0	0.0	(0.0 - 1.9)	0	0.0	(0.0 - 1.9)	0	0.0	(0 - 1.93)
40-44	181,513	0	0.0	(0.0 - 2.1)	0	0.0	(0.0 - 2.1)	0	0.0	(0 - 2.12)
45-49	186,253	10	5.3	(2.8 - 9.7)	1	0.6	(0.1 - 3.1)	0	0.0	(0 - 2.06)
50-54	218,713	10	4.4	(2.4 - 8.3)	3	1.5	(0.5 - 4.2)	3.2	1.5	(0.51 - 4.17)
55-59	254,615	10	4.0	(2.2 - 7.3)	4	1.7	(0.7 - 4.2)	14	5.5	(3.25 - 9.19)
60-64	193,308	14	7.3	(4.3 - 12.2)	9	4.4	(2.3 - 8.5)	24	12.3	(8.24 - 18.3)
20-64	1,799,340	56	3.1	(2.4 - 4.0)	18	1.0	(0.6 - 1.6)	41	2.3	(1.67 - 3.08)
45-64	852,889	44	5.1	(3.8 - 6.9)	17	2.0	(1.3 - 3.2)	41	4.8	(3.53 - 6.5)

*Estimated number of patients.

†95% confidence interval for the prevalence.

Table 3. Comparison of prevalence of dementia per 100,000 in the 30 to 64 year age group among studies

Authors	Year	Country	Place	Age range	Population at risk	n	Prevalence	Target
Mölsä et al.[21]	1982	Finland	Turku	45-54		10	51.0	all dementia
				55-64		24	144.0	
Sulkava et al.[22]	1985	Finland		30-64	6120	2	32.7	severe dementia
Schoenberg et al.[23]	1985	USA	Mississippi	45-64	5489	1	18.2	severe dementia
Kokmen et al.[15]	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.[24]	1993	UK	Northern Health Region	45-64	655,800	227	34.6	AD
Ohshiro et al.[2]	1994	Japan	Tottori	40-64	209,621	100	81.4	all dementia
Ratnavalli et al.[16]	2002	UK	London	45-64	326,019	59	81.0	all dementia
Harvey et al.[17]	2003	UK		30-64	240,766	130	54.0	all dementia
Rosso et al.[25]	2003	Netherlands	Zuid-Holland	30-59	1,435,769	21	1.5	FTLD
Present study	2006	Japan	Ibaraki	20-64	1,799,340	761	42.3	all dementia

Abbreviations: AD, Alzheimer Disease; VaD, vascular dementia; DLB, dementia with Levy bodies; FTLD, frontotemporal lobar degeneration

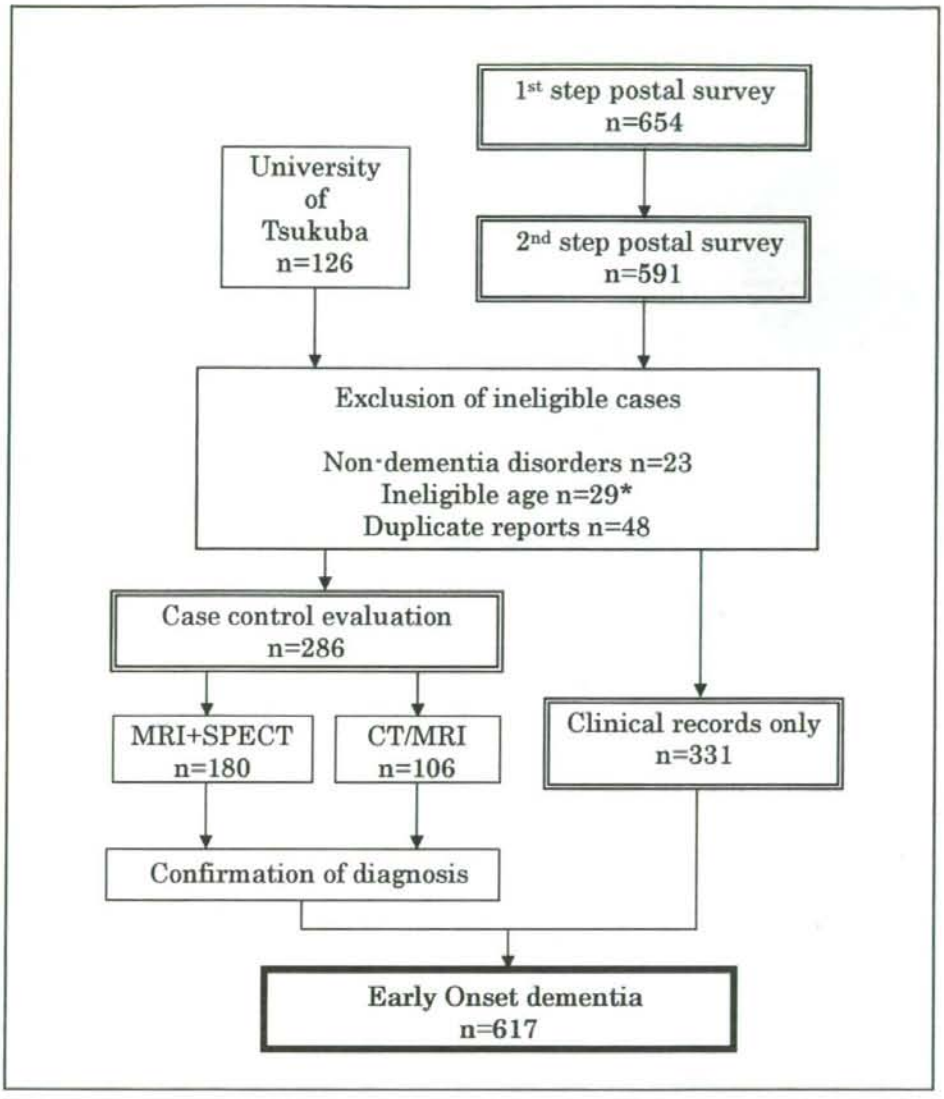

Figure 1. Flow chart indicating sources of identification for prevalent cases of pre-senile dementia in Ibaraki Prefecture.

*Subjects who had dementia starting before the age of 65 years but who were over 65 at the time of the study.

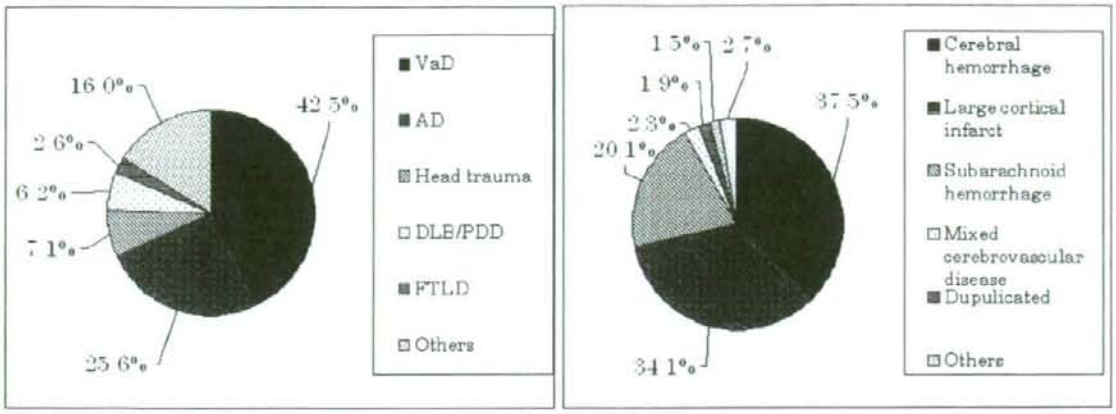

Figure 2. Distribution of diagnoses and subtypes of vascular dementia.