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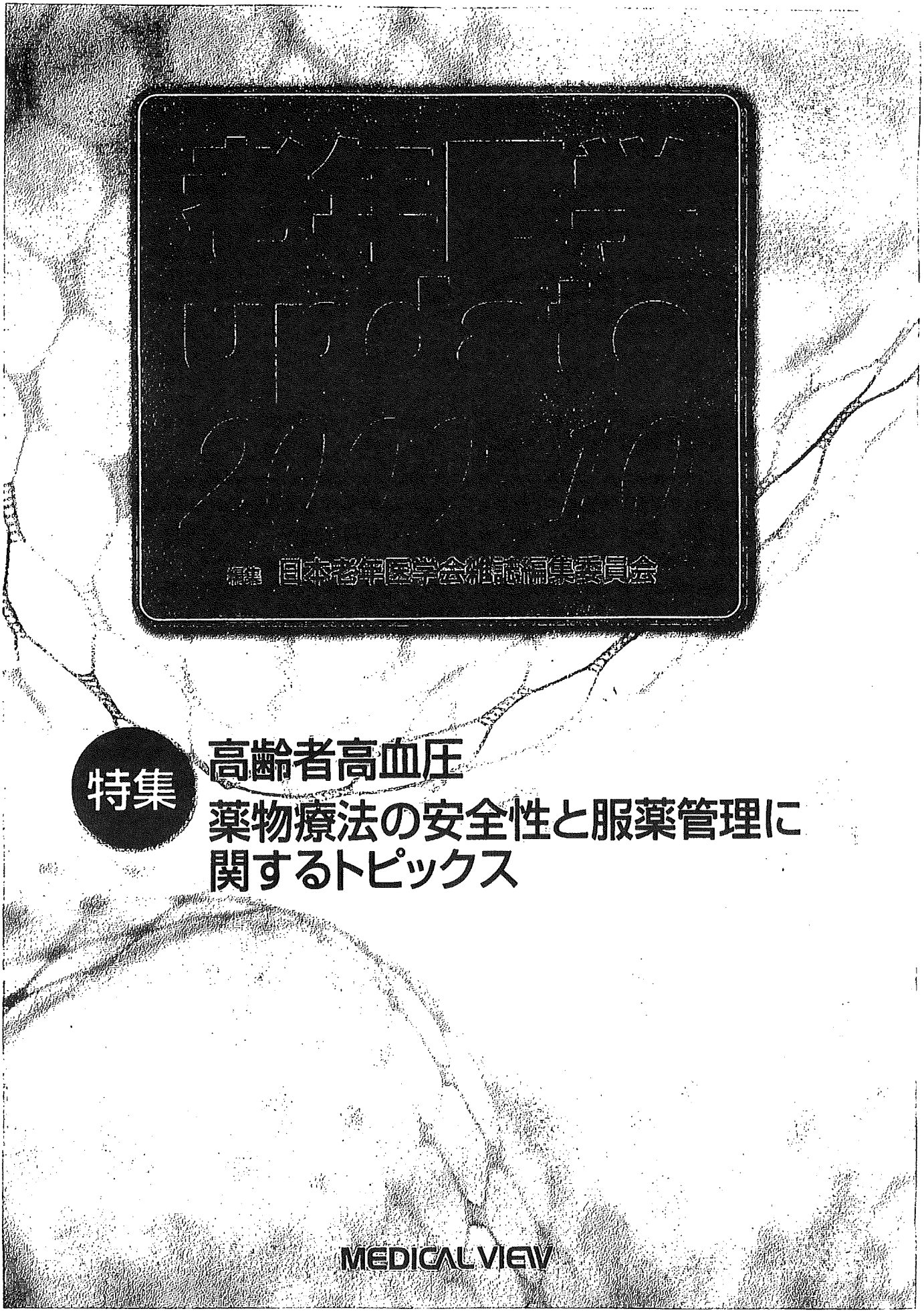
## Abstract

The purpose of long-term longitudinal epidemiological studies is to follow a certain cohort longitudinally, and collect detailed data on age-related changes in physical functions and mental activities. Longitudinal epidemiological studies are important not only to clarify the health problems associated with aging and the changes accompanying normal aging, but also to investigate the prevalence, risk factors, prevention, and early diagnosis of geriatric diseases such as dementia and osteoporosis. The National Institute for Longevity Science-Longitudinal Study of Aging (NILS-LSA) started in 1997. The participants in the NILS-LSA of the first wave were 2,267 men and women aged 40 to 79 years, randomly selected from the NILS area. Seven participants were examined every day at the NILS-LSA examination center, and followed up every two years. The aging process is assessed by detailed questionnaires and examinations including clinical evaluation, physiological functions body composition and anthropometry, physical functions, nutritional survey, and psychological assessments. The effects of genotypes, physical and psychological factors, and life-style and environment factors on aging and geriatric diseases were investigated by longitudinal analysis of these detailed and extensive data. In this review, methodologies of longitudinal study on aging and an outline of the system and examinations of the NILS-LSA are shown. The various results from the NILS-LSA research are also presented.

## Key words

Longitudinal study, Aging, Geriatric disease, Prevention, Healthy longevity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# Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community

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## SUMMARY

**Background** The results of previous reports estimating the prevalence of mild cognitive impairment (MCI) have varied widely according to the criteria used to define MCI.

**Methods** We assessed the cognitive function of Japanese community-dwelling individuals ≥65 years old and attempted to estimate the prevalence of four MCI subtypes (amnestic single, amnestic multiple, nonamnestic single, and nonamnestic multiple) using two cutoffs (1 and 1.5 SD) below normative standard. Presence of apolipoprotein E4 allele (APOE4), which is known as a strong risk factor for AD, is reportedly associated with high risk of conversion from MCI to AD. We therefore calculated the frequency of APOE4 carriers for each MCI subtype.

**Results** Initially 1888 (70%) of 2698 baseline samples participated, and 1433 (53%) subjects who had complete clinical data including APOE typing remained for the final analysis. The prevalence of MCI subtypes varied within the range of 1.7–16.6%, depending on the criteria applied. Prevalence of MCI was higher using a cutoff at −1.0 SD than at −1.5 SD, and prevalence of amnestic MCI single at −1.5 SD was lowest among all subtypes of MCI. Frequency of APOE4 was higher for amnestic MCI than for non-amnestic MCI or the cognitively normal group.

**Conclusion** The prevalence of MCI was highly dependent on the diagnostic criteria applied. A higher frequency of APOE4 in participants with amnestic MCI subtype suggested a greater risk of future AD. For future interventions to delay the onset of dementia, targeting individuals with amnestic MCI multiple at −1 SD might be desirable. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — MCI; pre-dementia; community; prevalence; APOE

## INTRODUCTION

Mild cognitive impairment (MCI) has been used to describe a distinct state of abnormal cognition that does not amount to dementia, but is distinguishable from normal cognitive decline associated with aging (Petersen, 1995). Although the MCI defined by Petersen (amnestic MCI single) is assumed to represent a core subtype of MCI and prodromal of dementia, evidence against this has been raised by community studies. For example, prevalence in community-based cohort was very low compared to the established incidence rate of Alzheimer disease (AD) (Jungwirth *et al.*, 2005). Indeed, prevalence rates varied widely in more than 20 reported community-based epidemiological studies of MCI and similar conditions have been reported, related in part to the different diagnostic criteria applied (Panza *et al.*, 2005). A more complete definition of MCI has recently been proposed, including the consideration of multiple types of cognitive impairment in addition to

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the memory impairment that characterizes amnestic MCI. This approach distinguishes four clinical subtypes: amnestic MCI single; amnestic MCI multiple; non-amnestic MCI single; and non-amnestic MCI multiple (Petersen *et al.*, 2004). To the best of our knowledge, only two epidemiological studies employing this newclassification of MCI have been published (Jungwirth *et al.*, 2005; Busse *et al.*, 2006).

The significance of the entity of MCI depends on a high specificity and sensitivity for conversion to dementia, including AD. In other words, the significance depends on predictive validity. However, there is currently no consensus with respect to specific thresholds for cognitive performance defining the diagnosis of MCI. For cognitive domains including memory, both performance worse than 1.0 and 1.5 standard deviation (SD) below the mean for those of similar age and education have been applied in previous studies (Busse *et al.*, 2003; Jungwirth *et al.*, 2005).

It is likely that several clinical and etiological heterogeneities exist between subtypes of MCI (Petersen *et al.*, 2004). However, amnestic MCI appears most closely linked with AD, sharing clinical and pathological features (Petersen *et al.*, 2006), including increased plasma levels of amyloid beta-protein A$\beta$42 (Assini *et al.*, 2004) which is the major pathogenic event of AD and the association between plasma A$\beta$40 concentration and extent of white matter hyperintensity on MRI (Gurol, 2006). In addition, some clinic-based researches have shown a relationship between possession of APOE4 and risk of conversion from MCI to AD (Petersen *et al.*, 1995; Devanand *et al.*, 2005). Data on APOE4 frequency for each subtype of MCI could therefore provide some information about risk of AD conversion and associated clinical characteristics.

We attempted to estimate the prevalence of MCI subtypes using two thresholds (1.0 and 1.5 SD below age-, sex- and education-matched means) and to determine the cross-sectional frequency of APOE4 for each MCI subtype among a Japanese population of elderly individuals.

## METHODS

The present research was conducted in Tone town, which consists of 22 districts. On May 1, 2001, a total of 3083 inhabitants $\geq$65 years old lived in the town. These 3083 inhabitants were considered as the pool of potential candidates.

This research was conducted by seven psychiatrists and eight psychologists trained for this study by the authors, along with public health nurses. All study protocols were approved by the ethics committee of the University of Tsukuba (Miyamoto *et al.*, 2009).

### *First phase*

The general design of the project is shown in Figure 1. This was a cross-sectional study. The first phase was conducted between December 2001 and April 2002. Before baseline examination, a letter was sent to each potential candidate explaining the objectives of the project. Individuals with whom a local welfare commissioner could not meet or contact despite three telephone calls were excluded as uncontactable.

Each of the 22 districts was visited once a week to conduct group screenings (1 in the morning, 1 in the afternoon). In addition to group screenings at the 22 districts, we visited 44 individuals who were institutionalized in a long-term care facility and performed examinations using the methods described below.

*Assessment procedures.* Eligible subjects provided informed written consent to participate in the study. After providing informed consent, all participants underwent a screening interview.

*Demographics and medical and psychiatric issuesc.* The interview consisted of a structured questionnaire assessing age, sex, education and medical and psychiatric condition. Subjects were also asked to provide blood samples for routine testing and genotyping of APOE (Corder *et al.*, 1993).

*Mood status.* This interview was followed by the 15-item short version of the Geriatric Depression Scale (Brink *et al.*, 1982) for mood assessment. Subjects scoring $\geq$6 were considered to display depressive symptoms.

*Perceived memory difficulty.* Subjects were asked whether they had memory difficulties using the 19 items of the Deterioration de Cognitive Observe (DECO), which was originally developed to objectively assess memory difficulty (Ritchie *et al.*, 1992). Memory difficulties were considered present if the subject indicated problems on $\geq$1 item.

*Assessment of activities of daily living.* Basic abilities in activities of daily living (ADL) were measured using Nishimura's Activities of Daily Living (N-ADL) (1993), which determines the level of independence in five activities: walking/transferring; going outside;

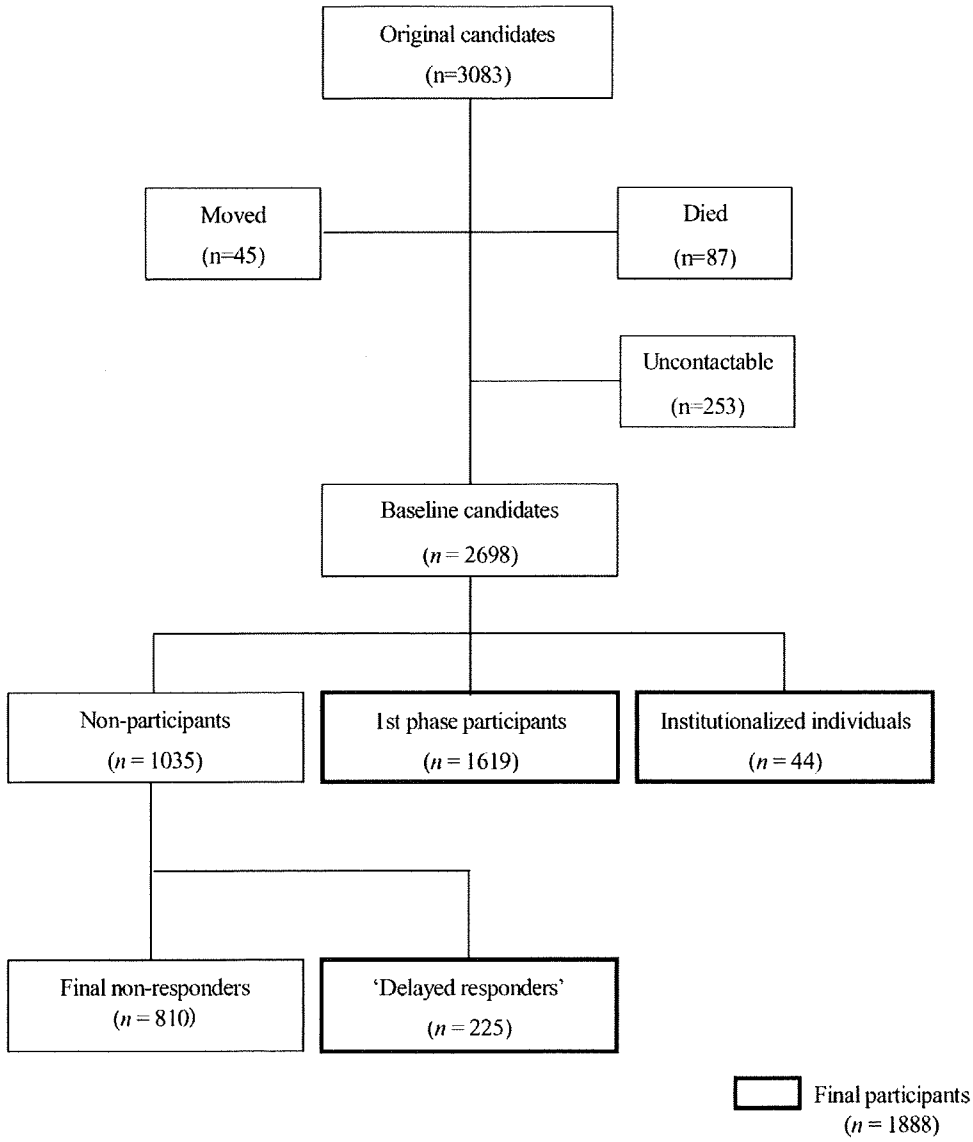


Figure 1. Flow chart indicating sources of identification for prevalent cases of MCI.

dressing/bathing; feeding; and toileting. Responders were considered functionally intact if no difficulties were reported on any of the 5 items of the NADL.

*Neuropsychological battery.* All participants underwent a group assessment that used a set of 5 tests measuring the following cognitive domains: attention; memory; visuospatial function; language; and reasoning. This set of tests was named the 5-Cog.

Attention was evaluated using a Japanese version of the set dependency activity (Sohlberg and Mateer, 1986), which assesses alternating attention. A Category Cued Recall test (Grober *et al.*, 1988) was used to assess memory ability. The Clock Drawing test, which requires subjects to draw the hands of a clock to depict the time at 'ten after eleven' (Freedman *et al.*, 1994), was used to assess visuospatial function. Language ability was examined using a category fluency test (Soloman and Pendlebury, 1998). The similarity subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) was employed to assess abstract reasoning ability.

This cognitive assessment was conducted in a group setting (maximum, 50 participants) by an examiner with the use of a projector. All participants were asked to record their answers on an answer sheet. Mean duration of the 5-Cog examination was 35 min. For participants who had difficulty understanding the tasks or impaired hearing or vision, the examination was conducted using an individual version of the 5-Cog in a face-to-face setting.

During the interview, subjects who could not respond to our instructions and/or some of the scales due to obvious cognitive impairment were also identified.

*Consensus diagnosis.* After each assessment, our team reviewed the functional, medical, neurological, psychiatric and neuropsychological data and reached a consensus regarding the presence or absence of dementia by diagnosis according to DSM-IV (American Psychiatric Association, 1994) criteria. Only subjects who were not diagnosed with dementia were considered for a diagnosis of MCI.

### *MCI diagnostic criteria*

Criteria for MCI were retrospectively applied among non-demented individuals after the consensus conference. Consistent with the standard criteria, for all subtypes of MCI described below, subjects considered for MCI were required to have: (1) objective impairment in $\geq 1$ cognitive domain based on the average of scores on neuropsychological measures within that domain and 1 SD and 1.5 SD cutoffs using normative corrections for age, years of education, and sex; (2) essentially preserved ADL(defined above); (3) presence of memory complaints (defined above); and (4) no diagnosis of dementia at the consensus diagnosis.

First, for our subtype of amnestic MCI single, memory impairment was defined as a score less than 1 or 1.5 SD below the demographically corrected mean on the category cued recall test, and performance on scores from all other cognitive domains (i.e. attention, language, visuospatial and reasoning) was required to fall within normal limits (more than 1 or 1.5 SD below the demographically corrected mean). Second, amnestic MCI multiple was diagnosed in the presence of memory impairment and impairment in one or more cognitive domains. Third, diagnosis of non-amnestic MCI single required cognitive impairment in a single non-memory domain and performance on scores in all other cognitive domains falling within normal limits. Finally, non-amnestic MCI multiple was diagnosed if impairment was seen in $\geq 2$ of the four non-memory domains, and if the memory domain score was within normal limits. We thus estimated the prevalence of eight forms (2 cutoffs $\times$ 4 subtypes) of MCI.

### *Second phase (investigation of delayed-responders)*

At the completion of the first phase, we had identified a total of 1035 non-participants who were contacted but had refused to participate, excluding the above-defined uncontactable individuals. As we desired to make this study representative, a door-to-door survey of non-participants was attempted to enroll as many participants as possible.

This portion of the phase was conducted with the aid of general practitioners and local welfare commissioners (persons vested with promoting social welfare in each local area), in the hope that their invitations would encourage participation of newcomers from among non-participants. They contacted and explained our project to individuals appearing on the non-participants list, with 225 non-participants subsequently agreeing to participate. These subjects were considered as 'delayed responders'. Our team visited the home of each delayed responder and conducted the same interview and tests that had been used in the first phase. The individual version of the 5-Cog was used for cognitive assessment. After each assessment, the case was discussed on the basis of the consensus diagnosis described above.

We did not ask the 'delayed responders' and 44 institutionalized individuals enrolled in the first phase to provide blood samples for genotyping of APOE because of the difficulty in collection and delivery of blood samples for laboratory examination.

*Statistical analysis.* For normative data, we excluded data from participants who did not complete the series of interview and examinations or had been diagnosed with dementia. Test–retest reliability of the 5-Cog was confirmed (Miyamoto *et al.*, 2009).

The characteristics and cognitive status of participants were analyzed using a $t$-test and $\chi^2$ test for continuous and categorical variables, respectively. We show the frequency of each MCI subtype as percent prevalence. The significance level was set at $p < 0.05$. Data were analyzed using SPSS 15.0J software (SPSS, Chicago, IL, USA).

## RESULTS

### *Study sample*

Of the 3083 potential candidates, 132 were excluded (Figure 1). Specifically, 87 had died and 45 had moved

before initial examination. An additional 253 residents were 'uncontactable individuals'. The remaining 2698 residents were considered as candidates at the baseline. Of the 1035 residents who initially refused to participate (non-participants), 225 became 'delayed responders'. As a result, 1888 (1619 first study and 225 'delayed responders' and 44 institutionalized individuals) (70%) of the 2698 baseline candidates were enrolled.

### *Prevalence of MCI*

As a result of consensus diagnosis, we estimated a prevalence of 4.5% for any type of dementia combined among the 1888 participants. We excluded 186 subjects of the first phase participants who had been diagnosed with dementia and/or refused APOE typing. As described, 225 'delayed responders' and 44 institutionalized individuals did not provide blood samples for APOE typing.

Consequently, 1433 (53%) of the 2698 candidate subjects remained for the final analysis. The final subjects had complete data including APOE typing and were not demented. Basic data for the subjects are shown in Table 1, and prevalence of the eight subtypes of MCI among subjects are shown in Table 2.

The main findings were as follows: (1) prevalence of MCIs ranged from 1.7% to 16.6%, depending on the diagnostic criteria applied, with the lowest prevalence for the original MCI (amnestic MCI single −1.5 SD); (2) when cutoffs of −1.0 SD and −1.5 SD were used, 18.9% and 38.9% of study participants were operationally diagnosed with some subtype of MCI, respectively; (3) prevalence of MCI using a cutoff of −1.0 SD was 1.5–3.5 times higher than for using −1.5 SD for the four MCIs; (4) the prevalence of amnestic MCI multiple was higher than the prevalence of amnestic MCI single, and MCI multiple at −1.0 SD displayed the highest prevalence (11.0%).

### *Frequency of APOE4*

APOE genotyping revealed that 19.9% of the 1433 participants were APOE4 carriers (2/4, 3/4 or 4/4). Frequencies of APOE4 for each subtype of MCI are shown in Table 3. Frequency was higher for the combined group of any type of MCI than for the cognitively normal group.

We first employed the analysis of multiple comparison among all four MCI subtypes and non-MCI, however the analysis showed no significant difference. Then, frequency was compared among normal, amnestic MCI (single and multiple) and non-amnestic MCI (single and multiple) groups using $\chi^2$ analyses with Ryan's multiple comparison procedure as a post hoc analysis. As a whole, the highest frequency was found in the amnestic MCI group (single and multiple) (Figure 2)

For the amnestic MCI group, the highest frequency of APOE4 (39.5%) was found in the multiple −1.5 SD subtype, whereas the lowest frequency (25.0%) was found in the single −1.0 SD subtype. The frequency for Petersen's original MCI (single −1.5 SD) was 32.0%. Frequency was higher for a cutoff of −1.5 SD than for −1.0 SD for all MCIs other than non-amnestic MCI multiple.

## DISCUSSION

### *General*

The sample size in the present study seems comparable to the largest studies among previously

Table 1. Demographic characteristics

| Characteristic | Overall group | APOE ε4 non-carrier | APOE ε4 carrier | *P* |
|---|---|---|---|---|
| | (*n* = 1433) | (*n* = 1148) | (*n* = 285) | |
| Age, years | 73.6 ± 5.8 | 73.6 ± 5.7 | 73.6 ± 5.8 | 0.882 |
| Female, *n* (%) | 844 (58.9) | 670 (58.4) | 174 (61.1) | 0.409 |
| Years of education | 10.0 ± 2.6 | 10.0 ± 2.6 | 10.0 ± 2.7 | 0.792 |
| GDS score | 2.9 ± 2.6 | 2.9 ± 2.6 | 2.7 ± 2.6 | 0.190 |
| N-ADL score | 49.7 ± 1.3 | 49.7 ± 1.3 | 49.7 ± 1.2 | 0.805 |
| IADL score | 5.2 ± 1.6 | 5.1 ± 1.6 | 5.2 ± 1.6 | 0.872 |
| BMI | 22.8 ± 3.2 | 22.9 ± 3.3 | 22.7 ± 3.0 | 0.368 |
| Alcohol consumption, *n* (%) | 493 (34.4) | 396 (34.5) | 97 (34.0%) | 0.876 |
| Smoking, n (%) | 501 (35.0) | 405 (35.3) | 96 (33.7%) | 0.600 |

Values represent mean ± SD.
BMI = body-mass index; GDS = Geriatric Depression Scale; IADL = instrumental activities of daily living; N-ADL = Nishimura's activities of daily living.


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Table 2. Baseline prevalence of 4 types of MCI

| MCI subtype | Severity level of MCI SD[‡] | Baseline prevalence | |
|---|---|---|---|
| | | *n* | % |
| Amnestic type | | | |
| single | 1.0 | 44 | 3.1% |
| | 1.5 | 25 | 1.7% |
| multiple | 1.0 | 157 | 11.0% |
| | 1.5 | 38 | 2.7% |
| Non-amnestic type | | | |
| single | 1.0 | 238 | 16.6% |
| | 1.5 | 164 | 11.4% |
| multiple | 1.0 | 118 | 8.2% |
| | 1.5 | 44 | 3.1% |
| All subtypes of MCI | | | |
| | 1.0 | 557 | 38.9% |
| | 1.5 | 271 | 18.9% |
| Non-MCI (no impairment in cognitive domains) | | | |
| | 1.0 | 876 | 61.1% |
| | 1.5 | 1162 | 81.1% |

[‡]Different MCI subtypes were determined according to different severity levels: cognitive performance 1.0 SD and 1.5 SD below the means of age-, education- and sex-matched control subjects.

reported population-based prevalence studies of pre-dementia syndromes including MCI from Western countries (Panza *et al.*, 2005). About half of these studies used amnestic MCI single as the diagnostic criteria, and most showed prevalence rates <6%. Our prevalence rates of 3.1% and 1.7% (−1 SD, −1.5 SD) for amnestic MCI single appears lower in comparison with previous results. However, we stand by the validity of our results on the following grounds. Age, educational level and gender have been reported as related to the prevalence of pre-dementia, but some of the previous studies estimating prevalence did not control for such factors (Panza *et al.*, 2005). Controlling for these factors might have contributed to the lower values. To the best of our knowledge, only two previous studies have identified MCI subtypes using similar methods to the present (Busse *et al.*, 2003; Jungwirth *et al.*, 2005). General findings of the current study resembled those of the two studies. Our estimated prevalence of MCIs, including amnestic MCI single, thus appear plausible.

Regarding APOE4 frequency for Japanese, a little less than half of AD patients are known to have at least one APOE4 allele and frequency is about three-fold that in normal controls (Ueki *et al.*, 1993; Asada *et al.*,

Table 3. Prevalence of APOE ε4 alleles

| APOE ε4 alleles | Amnestic type | | Non-amnestic type | | All subtypes of MCI | Non-MCI[†] |
|---|---|---|---|---|---|---|
| | Single | Multiple | Single | Multiple | | |
| MCI subtypes, 1.0 SD below mean[‡] | | | | | | |
| ε4− | 33 (75.0) | 113 (72.0) | 192 (80.7) | 96 (81.4) | 434 (77.9) | 714 (81.5) |
| ε4+ | 11 (25.0) | 44 (28.0) | 46 (19.3) | 22 (18.6) | 123 (22.1) | 162 (18.5) |
| MCI subtypes, 1.5 SD below mean[‡] | | | | | | |
| ε4− | 17 (68.0) | 23 (60.5) | 124 (75.6) | 37 (84.1) | 201 (74.2) | 947 (81.5) |
| ε4+ | 8 (32.0) | 15 (39.5) | 40 (24.4) | 7 (15.9) | 70 (25.8) | 215 (18.5) |

Values represent number (percentage).
[†]No impairment in cognitive domains.
[‡]Different MCI subtypes were determined according to different severity levels: cognitive performance 1.0 SD and 1.5 SD below means of age-, education- and sex-matched control subjects.


Figure 2. Proportion with APOE ε4 alleles between non-MCI, MCI-amnestic type and MCI-non amnestic type groups and between non-MCI, MCI-single domain impaired and MCI-multiple domains impaired groups $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.



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1996). A frequency of 18.5% APOE4 for non-MCI participants thus appears similar to that for healthy Japanese elderly individuals, and the 39.5% for amnestic MCI multiple −1.5 SD subjects seems a little less than the frequency for Japanese AD patients. As described below, individuals with amnestic MCI are assumed to be likely to convert to AD, so a value of 39.5% appears plausible. To the best of our knowledge, the only community-based study of MCI estimating frequency of APOE4 carriers found an association between APOE4 and original amnestic MCI (Lopez *et al.*, 2003). In that study, APOE4 frequencies for amnestic MCI and healthy participants were 33% (12/40) and 20% (101/552), respectively. These results closely resemble our own and support the validity of results from the APOE study.

*Amnestic vs non-amnestic MCI*

According to the consensus of the Key Conference on MCI, amnestic MCI single is presumably caused by prodromal AD, and amnestic MCI multiple by AD or vascular dementia (VD) (Winblad *et al.*, 2004). In fact, two community-based longitudinal studies have shown that amnestic MCI is likely to convert to AD (Busse *et al.*, 2006; Fischer *et al.*, 2007). However, neither of these two studies reported APOE4 frequency. Conversely, non-amnestic MCI single is presumably caused by dementia with Lewy bodies (DLB) or VD, and non-amnestic MCI multiple by DLB or frontotemporal dementia. However, the course of non-amnestic MCI shown in the two studies was contradictory (Busse *et al.*, 2006; Fischer *et al.*, 2007).

Many clinic-based studies that have examined the utility of APOE4 in predicting AD conversion among amnestic MCI patients have shown affirmative results (Mosconi *et al.*, 2004; Devanand *et al.*, 2005). In the present study, comparison between the APOE4 frequency in combined amnestic-MCIs and the combined non-amnestic MCIs showed a statistically significant difference, however the analysis of multiple comparisons among all four MCI subtypes and non-MCI did not. The discrepancy appears to be attributable to small number of individuals with MCIs especially amnestic MCI single, however it may indicate the homogeneity of the amnestic MCI group (single plus multiple) and the non-amnestic group (single plus multiple). In any case, frequency of APOE4 was higher for the amnestic MCI group than for the non-amnestic group and normal elderly individuals, with similar frequencies for the latter two groups. Taking these findings together, amnestic- and non-amnestic MCI may differ in future course with respect to conversion to AD.

*Clinical significance of amnestic MCIs*

Among 4 subtypes of amnestic MCI, the highest prevalence ($n = 157$, 11.0%) was found for amnestic MCI multiple −1.0 SD, and this group showed relatively high APOE4 frequency (28.0%). Theoretically, the estimated number of individuals who will develop AD in future may be considerably larger for this subtype than for other MCI subtypes. Conversely, amnestic MCI multiple −1.5 SD ($n = 38$, 2.7%) showed the highest APOE4 frequency of 39.5%, not markedly different from that present in Japanese AD patients. On the basis of our experience, clearly distinguishing operationally diagnosed amnestic MCI multiple −1.5 SD from clinically diagnosed early dementia using DSM-IV criteria is difficult. Some individuals with our operational diagnosis of amnestic MCI multiple −1.5 SD could thus instead represent patients at the very early stages of AD.

Needless to say, cognitive impairment is milder for amnestic MCI multiple −1.0 SD than for amnestic MCI multiple −1.5 SD. For future community studies, providing a preventive intervention for amnestic MCI multiple −1.0 SD individuals might be desirable, while individuals with amnestic MCI multiple

KEY POINTS

- Prevalence of MCIs ranged from 1.7% to 16.6%, depending on the diagnostic criteria applied, with the lowest prevalence for the original MCI (amnestic MCI single −1.5 SD).
- Among normal, amnestic MCI (single and multiple) and non-amnestic MCI (single and multiple) groups, the highest frequency was found in the amnestic MCI group (single and multiple).
- The results of APOE4 frequency suggest that amnestic- and non-amnestic MCI may differ in future course with respect to conversion to AD.
- For future community studies, providing a preventive intervention for amnestic MCI multiple −1 SD individuals might be desirable, while individuals with amnestic MCI multiple −1.5 SD could represent the best target for early detection of AD.

−1.5 SD could represent the best target for early detection of AD.

Finally, it is important to test for possible non-response bias for this kind of study, thus we have examined this issue elsewhere (Miyamoto *et al.*, 2009). This cross-sectional study of MCI was unable to evaluate positive predictive power for each subtype of MCI. Nevertheless, the present community-based study appears to provide useful information on MCI.

## CONFLICT OF INTEREST

None known.

## ACKNOWLEDGEMENTS

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# Prevalence and Causes of Early-Onset Dementia in Japan
## A Population-Based Study

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***Background and Purpose***—Few studies are available that have addressed the prevalence of early-onset dementia (EOD), including early-onset Alzheimer disease and other forms of dementia in Japan.

***Methods***—A 2-step postal survey was sent to all of the 2475 institutions providing medical or care services for individuals with dementia in Japan's Ibaraki prefecture (population, 2 966 000) requesting information on EOD cases. Data were then reviewed and collated.

***Results***—We identified 617 subjects with EOD. The estimated prevalence of EOD in the target population was 42.3 per 100 000 (95% CI, 39.4 to 45.4). Of the illnesses that cause EOD, vascular dementia was the most frequent (42.5%) followed by Alzheimer disease (25.6%), head trauma (7.1%), dementia with Lewy bodies/Parkinson disease with dementia (6.2%), frontotemporal lobar degeneration (2.6%), and other causes (16.0%).

***Conclusions***—The prevalence of EOD in Japan appeared to be similar to that in Western countries with the notable exception that vascular dementia was the most frequent cause of EOD in Japan. **(*Stroke*. 2009;40:2709-2714.)**

**Key Words:** early-onset dementia ■ prevalence ■ vascular dementia

Patients with onset of dementia before the age of 65 years, defined as early-onset dementia (EOD), endure significant personal psychological problems and are responsible for a considerable societal economic burden. Clinicians have been urged to improve their recognition of, familiarity with, and understanding of EOD.[1]

In Japan, previous studies of EOD have reported relatively small sample sizes due to inclusion of patients assessed only at hospitals and memory clinics.[2–4] To more accurately estimate the prevalence of EOD as well as the individual diseases responsible, it is necessary to include all diagnosed cases in a region. Therefore, we aimed to estimate the prevalence of EOD in Japan by a 2-step survey capturing all known cases in a single large prefecture. This study was approved by the ethics committee of the University of Tsukuba and conducted with the aid of the Department of Health and Welfare of Ibaraki Prefecture.

## Materials and Methods

The study was conducted in Ibaraki Prefecture, which is located 30 km north of the Tokyo metropolitan area, and has a population of approximately 2 966 000. This is the 11th largest of the 47 prefectures with an equal ratio of males and females and equivalent demographic composition to other prefectures in terms of proportion of working persons and socioeconomic status. EOD subjects were defined as those whose age at onset and age on April 1, 2006 (national census day) was <65 years.

### Step 1

For the first step, a questionnaire was mailed to all kinds of medical institutions (including psychiatric and neurological outpatient departments), home-visit nursing services, long-term care insurance-related facilities, local branches of departments of prefectural health and welfare for the elderly, and local welfare commissioners. Each institution was asked, "How many EOD patients did you care for between April and October 2006?" A fact sheet detailing the diagnosis of dementia based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised[5] was also sent to each institution. It is worth noting that in Japan, all care services for community-dwelling elderly and individuals with EOD are provided by publicly funded long-term care insurance, which is separate from medical care insurance. Municipal long-term care insurance approval boards certify whether an applicant is eligible for long-term care insurance based on the results of screening for his or her mental and physical condition and the assessment report documented by a doctor in charge of him or her.

### 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[6]; dementia with Lewy bodies and Parkinson

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**Table 1. Response Rates of the Postal Surveys**

| | Step 1 | | | Step 2 | | | |
|---|---|---|---|---|---|---|---|
| Institutions | Target Populations | n* | Response Rate, % | Target Populations | n | Response Rate, % | Reported Cases |
| Hospitals with >200 beds† | 54 | 53 | 98.1 | 22 | 21 | 95.5 | 203 |
| Hospitals with <200 beds | 113 | 106 | 93.8 | 21 | 16 | 76.2 | 186 |
| Clinics | 1269 | 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 | 2475 | 2202 | 89.0 | 285 | 245 | 86.0 | 717 |

*No. of respondent institutions.
†Hospitals with >200 beds include the University of Tsukuba.

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 Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised criteria for dementia, but not fulfilling criteria for any of the previously mentioned diagnostic categories, were assigned to the "other" category.

Answers for the additional information for cases reported from nonmedical 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 Steps 1 and 2, up to 3 reminder letters were sent to institutions that had failed to respond 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 cases and specialized in medical practice for dementia or stroke. For approximately 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 MRI, CT, and single photon emission CT.

## Statistical Analysis

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: (1) the reciprocal of the product of the response rate for the first and second steps (sample weight) was calculated; and (2) 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% CIs based on 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 $\chi^2$ tests or Fisher 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 nondementia disorders (n=4). None of these

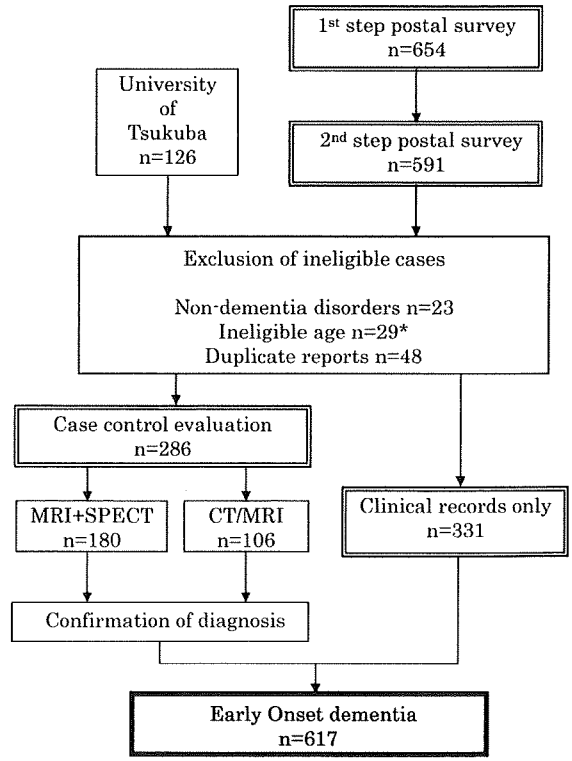


**Figure 1.** Flow chart indicating sources of identification for prevalent cases of presenile dementia in Ibaraki Prefecture. *Subjects who had dementia starting before the age of 65 years but who were >65 years at the time of the study.

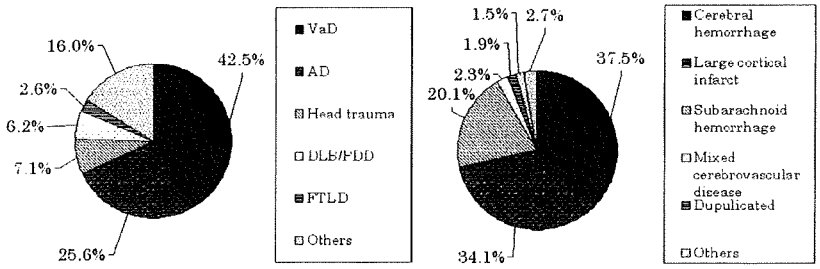


**Figure 2.** Distribution of diagnoses and subtypes of VaD.

patients were considered to have had concomitant EOD. In addition, 29 patients were excluded because their age on the census day was >65 years, although their age at onset of dementia was <65 years. In some instances, 2 or more institutions contributed reports on the same individual cases: 36 individuals from 2 institutions, 2 individuals from 3 institutions, and one individual from 4 institutions. Five cases received different diagnoses: 4 with AD also classified as dementia with Lewy bodies (DLB) and one 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 healthcare 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 the census day of this group was 56.9 years (SD, 7.3; range, 22 to 64 years) and the mean age at onset of dementia was 53.4 years (7.9; 18 to 64 years).

**Table 2. Age-Specific Prevalence per 100 000 for the Causes of Dementia in Ibaraki Prefecture, Japan, April 1, 2006**

| | | All Dementia | | | VaD | | | AD | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age Range, Years | 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 |

| | | Head Trauma | | | Frontotemporal Lobar Degeneration | | | DLB/Parkinson Disease With Dementia | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age Range, Years | 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 | 0–2.36 |
| 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 no. of patients.
†95% CI for the prevalence.

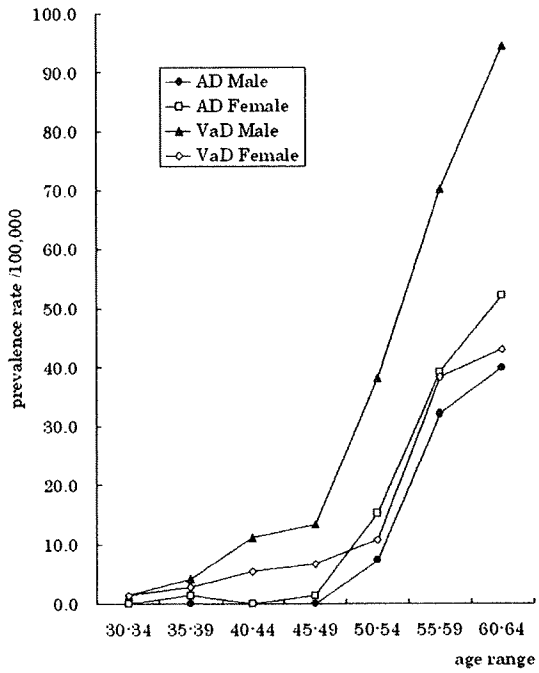


**Figure 3.** Age- and sex-specific prevalence of AD and VaD.

Of the illnesses causing EOD, VaD was the most frequent (42.5%) followed by AD (25.6%), head trauma (7.1%), DLB/Parkinson disease with dementia (6.2%), frontotemporal lobar degeneration (2.8%), and others (16.0%; Figure 2). The frequency of the illnesses causing EOD was calculated from 2 subgroups; quality control detailed evaluation group (n=286) and clinical records only group (n=331; Figure 1). Subgroup analysis did not change the overall order of the 3 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 frontotemporal lobar degeneration (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 (eg, cerebrovascular hemorrhage and large cortical infarct; 2.0%), other VaD (eg, 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 years was 42.3 per 100 000 (95% CI, 39.4 to 45.4). From the age of 30 onward, 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 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 late-onset dementia 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

**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, Years | 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 |
| Ohishiro 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 | Frontotemporal lobar degeneration |
| Present study | 2006 | Japan | Ibaraki | 20–64 | 1 799 340 | 761 | 42.3 | All dementia |

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 presenile group. This finding indicates that VaD as an illness causing dementia has likely decreased in the elderly but not in the presenile 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 presenile and senile populations.

Another important issue is the difference in the pathogenesis of stroke between presenile and senile populations. The Japanese Standard Stroke Registry Study (JSSRS) used data from 16 630 patients with stroke from many centers.[13] According to the JSSRS report, the peak age group for occurrence of subarachnoid hemorrhage is 50 to 59; for cerebral hemorrhage, it is 60 to 79; and for lacunar infarction, it is 70 to 79. This report indicated that cerebral and subarachnoid hemorrhage cause the majority of presenile strokes, whereas lacunar infarction is the main cause of senile stroke. It was also reported that among the various vascular illnesses causing VaD in the senile population, lacunar stroke had decreased in frequency, whereas no reduction in the proportion of cerebral and subarachnoid hemorrhage has yet been reported.[14] Hence, hemorrhages have been assumed to be the most common causes of presenile 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 2 decades ago, a Finnish study[18] showed the incidence of stroke for Japanese presenile men as more than twice as high as that for the white presenile population of men and women combined. As described here, the incidence of stroke in the Japanese presenile group has probably not decreased. In addition, the results of the current study (Figure 3) 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 presenile 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 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 presenile dementia in a large community sample (Table 3). Case ascertainment was also more thorough, including both medical institutions and nonmedical (long-term care insurance) 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 suboptimal 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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## Disclosures

None.

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Clinical Study

# Dementia and mild cognitive impairment among non-responders to a community survey

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**Abstract**

We aimed to estimate the prevalence of mild cognitive impairment (MCI) among elderly non-responders to a community-based survey. We conducted a two-phase, population-based cross-sectional study of community-dwelling individuals aged 65 years or older in Tone, located in central Japan. The first phase of the study consisted of physical and cognitive examinations of individuals who responded to the first recruitment (quick-responders), whereas the second phase included individuals who did not respond in the first phase (delayed-responders). We compared the prevalence of MCI and dementia between delayed-responders and quick-responders. Of the 2,698 potential candidates, 1,888 (1,619 quick-responders, 225 delayed-responders, and 44 nursing home residents) were enrolled (70.0%). The prevalence of MCI was 2.3-fold increased in delayed-responders compared to the quick-responders (OR = 2.27, 95% CI: 1.37–3.77, $p = 0.002$, aged $\leqslant 74$). In order to develop a method for the early detection of dementia, we must pay more attention to delayed-or non-responders.


*Keywords:* Cognitive function; Community survey; Long term care insurance; Mild cognitive impairment; Non-responder

## 1. Introduction

To avoid underestimating the prevalence of dementia in epidemiological studies, it is important to consider the non-responders.[1] Response rates decline with age and the cognitive states of non-responders are lower than responders.[2–4] Some recent studies have examined the cognitive functions of non-responders; individuals who do not respond to a community-based study. Norton et al. evaluated the characteristics of non-responders in a community survey of elderly individuals aged 75 years and older and reported that non-responders appeared to be disproportionately cognitively impaired.[5] In addition, Launer et al. compared cognitive functioning between non-responders and responders among community-dwelling elderly aged 65 years and more.[3] They reported that non-responders aged 74 years or younger, but not those aged 75 years and older, showed poorer performances on a cognitive test compared to responders. However, the results of non-responders are still inconsistent.[6]

During the last decade, there have been several attempts to distinguish abnormal cognitive impairment from normal cognitive decline associated with aging. Herein, the term mild cognitive impairment (MCI) is used to describe such transitional states. Currently, MCI[7] and Ageing-Associated Cognitive Decline (AACD)[8] are widely accepted definitions of the boundary states between normal aging and dementia. Although the reported conversion rate to dementia varies widely, individuals with MCI[9] and

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AACD[10] develop dementia at a rate of 10% per year and 28% over 3 years, respectively.

To our knowledge, the relationship between the prevalence of MCI and non-responders has not been examined in a relatively large community study. Thus, the aim of the present study was to compare the prevalence of MCI and dementia between responders and non-responders in a community-based study of the elderly.

## 2. Methods

We conducted the survey in Tone, a town consisting of 22 districts, in a rural area, Ibaraki, about 40 km northeast of central Tokyo, Japan. On 1 May 2001, 3,083 inhabitants aged 65 years and older (the potential candidates) lived in the town (15.7% of the total population of Tone). The proportion of the elderly in Tone was similar to that of the whole of Japan as of 2001.

Seven psychiatrists, eight psychologists and public health nurses were trained for the present study by the primary investigator. The protocol of this study was approved by the ethics committee of the University of Tsukuba.

### 2.1. The first phase

The first phase of the project (Fig. 1) was conducted from December 2001 to April 2002. Before the baseline examination, we sent a letter to each potential candidate and explained the project's objectives. After the study was explained to the individuals and written informed consent obtained, all responders underwent a screening interview. One week before the group screening, we telephoned each candidate and asked him or her to participate. We also asked the local welfare commissioners (*Minsei-iin*: persons who are vested with promoting social welfare in each local area) to recommend individual residents to participate in the research. The individuals with whom a local welfare commissioner could not meet or contact after three telephone calls were excluded from the study (hereafter referred to as uncontactable individuals).

We visited each of the 22 districts once per week and conducted group screenings. We also visited a nursing home and examined 44 individuals using the same procedures as follows.

### 2.2. Assessment procedures

#### 2.2.1. Demographics, medical and psychiatric factors

The interview consisted of a structured questionnaire recording age, sex and education and assessing previous medical and psychiatric diseases and dementia risk factors, including alcohol and tobacco consumption. We also measured the height and weight of each responder.

#### 2.2.2. Mood state

The interview was followed by the 15-item short version of the Geriatric Depression Scale (GDS) for mood assessment.[11] Those who scored six or more were considered to have depressive symptoms.

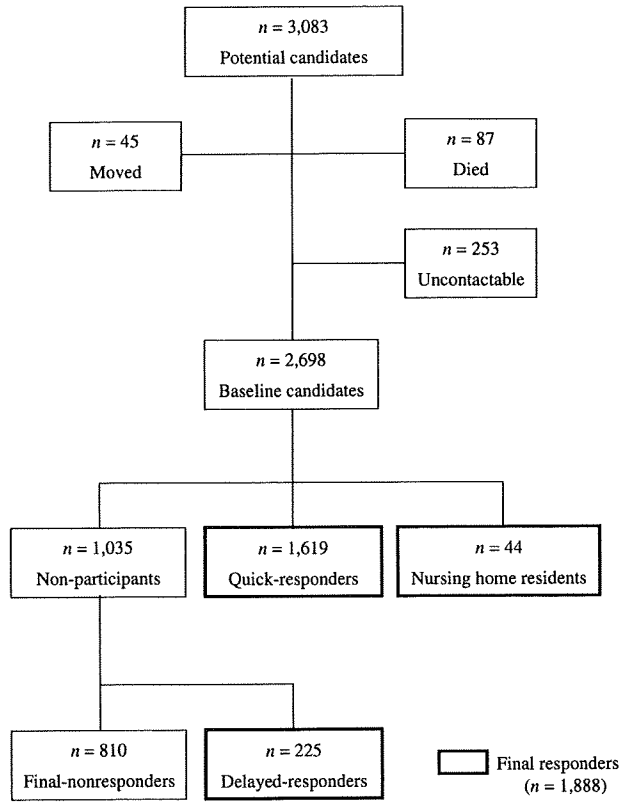


Fig. 1. Study population of the community-based survey conducted in Tone, Japan.

#### 2.2.3. Perceived memory difficulty

Responders were asked whether they had memory difficulties in general, as well as difficulties in specific areas according to the 19 items of the Détérioration Cognitive Observée (DECO), which was originally developed for an objective assessment of memory difficulty.[12] Responders were considered to have memory complaints if they indicated that they had problems on one or more of the items.

#### 2.2.4. Assessment of activities of daily living

Basic activities of daily living were measured using N geriatric rating scale for activities of daily living (N-ADL),[13] which determines the level of independence in five activities: walking/transferring, living area, dressing/bathing, eating and toileting. Responders were considered to be functionally intact if they reported no difficulty on any of the five items of the N-ADL.

#### 2.2.5. Neuropsychological assessment

After completing the interview, all responders underwent a group assessment which used a set of five tests measuring the following cognitive domains: attention, memory, visuospatial function, language and reasoning. We named this set of tests thereafter the 5-Cog. We evaluated atten-

tion by using a Japanese version of a set dependent activity.[14] The test assesses alternating attention, which refers to the capacity for mental flexibility that allows individuals to shift their focus of attention between tasks with different cognitive requirements. In this test, there were three rows on the page (top, middle and bottom) with three Chinese characters that meant "top", "middle" or "bottom". Some of the characters were placed in the incorrect rows. The responders were required to choose the characters that were placed in the correct rows. In order to assess the memory ability, we used a Category Cued Recall test.[15] A Clock Drawing test, which required the subjects to draw clock hands showing the time at " ten after eleven"[16] was used to assess visuospatial function. We examined language ability by using a category fluency test.[17] The subjects were asked to generate as many examples as possible in two minutes from the semantic category "animals". The total number of animals named was the score for the test. To assess abstract reasoning ability, we employed the similarity subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[18]

This cognitive assessment was conducted in a group setting (maximum 50 participants) by an examiner with the use of a projector. Each screening was supervised by about 10 members of our research team. The mean length of the 5-Cog examination was 35 minutes. For responders who had difficulty understanding the tasks or had impaired hearing or vision, we conducted the examination using an individual version of the 5-Cog in a face-to-face setting.

During the interview and examinations, we estimated the visual acuity, hearing and speech ability of each subject. We also identified those individuals who could not respond to our instructions and/or some of the scales because of obvious cognitive impairment.

### 2.3. Consensus diagnosis

After each assessment, a group of psychiatrists and neuropsychologists reviewed the functional, medical, neurological, psychiatric and neuropsychological data and reached a consensus regarding the presence or absence of dementia according to the DSM-IV criteria.[19]

#### 2.3.1. Mild cognitive impairment diagnostic criteria

Criteria for MCI were retrospectively applied to individuals without dementia after the consensus conference. Consistent with standard criteria, for all subtypes of MCI,[20] those considered for MCI were required to have: (i) a memory complaint (defined previously); (ii) objective impairment in at least one cognitive domain based on the average of the scores on the neuropsychological measures within that domain, and 1 standard deviation (SD) and 1.5 SD cut-off using normative corrections for age, sex and years of education; (iii) essentially preserved activities of daily living (defined above); and (iv) no diagnosis of dementia at the consensus conference.

We identified each subtype of MCI[21] to estimate the overall prevalence of MCI. First, for our subtype of MCI-amnestic, memory impairment was defined as a score less than 1 or 1.5 SD below the demographically corrected mean on the Category Cued Recall test, and performance on scores from all other cognitive domains (i.e. attention, language, visuospatial and reasoning) was required to fall within normal limits (score must be more than 1 or 1.5 SD below the demographically corrected mean).

The second subtype was classified as nonamnestic MCI single domain. The nonamnestic MCI single domain has a cognitive impairment in a single nonmemory domain and performance on scores in all other cognitive domains fell within normal limits.

Finally, a diagnosis of MCI-multiple cognitive domains with memory impairment was made if there was objective impairment on the memory domain score and if there was impairment on one or more cognitive domains. The diagnosis of MCI-multiple cognitive domains without memory impairment was assigned if there was impairment in two or more of the four nonmemory domains, and if the memory domain score was within normal limits. The classification into each MCI subtype was mutually exclusive.

### 2.4. The second phase – delayed-responders

At the completion of the first phase of the study, we identified a total of 1,035 non-responders who were contacted but who had refused to participate, excluding the uncontactable individuals as defined above. We attempted a door-to-door survey of those non-responders. The second phase of the study was conducted with the aid of general practitioners and local welfare commissioners. We asked them to contact and explain our project to the individuals who appeared on the non-responders list. Subsequently, between April and June 2002, 225 of the non-responders who did not respond to the first phase of the survey agreed to participate (hereafter referred to as delayed-responders). A psychiatrist (T.A.) and a psychologist visited each delayed-responder's home and conducted the same interview and examinations that were used in the first phase. The individual version of the 5-Cog was used for cognitive assessment. When we suspected that an individual had dementia, we used the same procedure to diagnose dementia as described above.

### 2.5. Long-Term Care Insurance

In Japan, care services for frail community-dwelling elderly individuals are provided by a public Long-Term Care Insurance (LTCI) system that was launched in April 2000.[22] Currently, many frail elderly individuals use services provided by the LTCI system. On 30 June 2001, the Tone town office approved our use of data from the LTCI system, provided we maintained anonymity of the participants and limited our use of the data to the present study. The data comprised demographic and medical information from all 263 individuals (131 quick-responders, 10 delayed-