associations is the concurrent deterioration of the brain regions responsible for cognitive and physical performance in the pre-dementia stage of aging. Small to relatively large deterioration of overall brain structures is observed by magnetic resonance imaging even in healthy older adults (Resnick et al., 2003). Such deterioration may lead to concurrent alterations in cognitive and physical performance in the pre-dementia stage. Because all the physical fitness tests used in the present study require refined brain control for initiation of the tasks, recruitment of muscles, and motor coordination in given constraints, it can be plausible that the deterioration of the brain affects not only cognitive function but also the quality of physical performance objectified by the physical fitness measures.

Based on the observed results, the present study offers a practical value of the physical fitness measures as objective means to assist identifying and monitoring early cognitive impairment in community-based regular checkups. Virtually, all the physical fitness tests used in the present study are simple and require no clinical resources or sophisticated devices. For example, the gait test, sit-to-stand test, and one-leg stand test need only a stopwatch and can be self-performed even at home. In addition, considering the significant association for each physical fitness measure, the five tests may not necessarily have to be performed all together. Rather, any one or a few tests can be selected in the regular checkups, depending on the physical functional status of individuals being tested. Incorporating the physical fitness measures into community-based regular checkups may add information to help earlier detection of cognitive impairment which can allow potential patients to receive effective medical treatments to prevent or slow the onset of dementia sooner. If this will be the case in the near future, it could bring a positive economic impact to society. Indeed, an estimation showed that if new treatment delaying the onset of Alzheimer's disease (AD) by 5 years will be available in 2015, it could result in the reduction of the projected Medicare costs of AD by 45.1% (from $627 billion to $344 billion) in 2050 in the United States (Sperling et al., 2011).

The strengths of the present study are the relatively large population-based samples, the choice of the cognitive instrument (i.e., MoCA) suitable for examining the differences in cognitive function in the participants free from apparent cognitive problems, the use of multiple objective measures of physical fitness, and the variety of confounding measures including the accelerometer-derived PAEE and other health-related scales such as the IADL and K6. In contrast, the present report has several limitations which are worth noting here. First, the sample of the present study might be biased to some extent by the exclusion of subjects (Figure 1). Specifically, subjects excluded due to the refusal or incompletion of the cognitive tests were younger and had a higher proportion of men than the remaining subjects (median age: 72 vs. 73 years, $p < 0.01$; percentage of men: 50.8 vs. 41.8%, $p < 0.001$). However, since the excluded subjects are considered to have relatively good status on both physical and cognitive functions, the influence of the exclusion on the observed associations may not be considerable. Also, subjects excluded due to the refusal of the physical fitness tests and the other incomplete measures had a higher proportion of men and lower MoCA scores than the present participants (percentage of men: 48.2 vs. 40.1%, $p < 0.005$; mean MoCA score: 21.8 vs. 22.4 years, $p < 0.001$). Nevertheless, the influence of this exclusion may also not be sizable because the excluded subjects presumably had relatively lower physical functioning than the present participants besides the lower cognitive function. Second, the relatively large samples of the present study did not allow us to perform neurological examination to determine older individuals with clinical cognitive impairment. Instead, we used the MMSE cut-off score of <24 which has been widely used to screen dementia in clinical and population-based studies (Holsinger et al., 2007). Finally, because the present study was performed in a single Japanese town, generalizability of the results to other regions is limited. Therefore, further community-based studies in other populations should be performed to overcome this limitation.

Conclusion

In summary, the present study first demonstrated the associations between five physical fitness measures and global cognitive function in Japanese community-dwelling older people without apparent cognitive problems, independent of age, sex, years of formal education, body mass index, and other confounding factors. The present results suggest that each of the five physical fitness measures has a potential ability as a single lifestyle-related marker of low cognitive function in older populations free from dementia and thereby can be used to help earlier detection of cognitive impairment in community-based preventive care of dementia. Future studies will be conducted to develop a specific screening method for early cognitive impairment in the pre-dementia stage with using these physical fitness measures.

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Key points

- There is a great need for identifying lifestyle-related markers which help detect subtle cognitive impairment in the preclinical or earlier phase of dementia.
- In the present study, each of the five physical fitness measures employed was linearly and positively associated with the Montreal Cognitive Assessment score in the present older adults without apparent cognitive problems, after adjusting for age, sex, education, body mass index, and other confounding factors.
- The results suggest the potential of each physical fitness measure as a single lifestyle-related marker of low cognitive function in the population, which can be useful in community-based preventive care of dementia.

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Thrombolytic therapy for stroke in patients with preexisting cognitive impairment

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Supplemental data at Neurology.org

ABSTRACT

Objective: We aimed to evaluate the influence of prestroke cognitive impairment (PSCI) on outcomes in stroke patients treated with IV recombinant tissue plasminogen activator (rtPA).

Methods: OPHELIE-COG was a prospective observational multicenter study conducted in French and Japanese patients treated with IV rtPA for cerebral ischemia. The preexisting cognitive status was evaluated by the short version of the Informant Questionnaire on Cognitive Decline in the Elderly. PSCI was defined as a mean score >3. The primary endpoint was a favorable outcome (modified Rankin Scale [mRS] score 0–1) after 3 months. Secondary endpoints were symptomatic intracerebral hemorrhage (sICH), mRS scores 0–2, and mortality at 3 months. We performed a pooled analysis with Biostroke and Strokdem.

Results: Of 205 patients, 62 (30.2%) met criteria for PSCI. They were 11 years older ($p < 0.001$). Although they had more sICH and were less frequently independent after 3 months, they did not differ for any endpoint after adjustment for age, baseline NIH Stroke Scale score, and onset-to-needle time: sICH (odds ratio [OR] 2.78; 95% confidence interval [CI] 0.65–11.86), mRS 0–1 (OR 0.82; 95% CI 0.41–1.65), mRS 0–2 (OR 0.62; 95% CI 0.28–1.37), death (OR 0.40; 95% CI 0.08–2.03). The pooled analysis found no association of PSCI with any endpoint.

Conclusions: Ischemic stroke patients with PSCI should receive rtPA if they are eligible. This conclusion cannot be extended to severe cognitive impairment or severe strokes.

Classification of evidence: This study provides Class IV evidence that in patients with PSCI presenting with acute ischemic stroke, IV rtPA improves outcomes. ***Neurology*® 2014;82:1–7**

GLOSSARY

CI = confidence interval; **IQCODE** = Informant Questionnaire on Cognitive Decline in the Elderly; **IQR** = interquartile range; **MMSE** = Mini-Mental State Examination; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PSCI** = prestroke cognitive impairment; **rtPA** = recombinant tissue plasminogen activator; **sICH** = symptomatic intracerebral hemorrhage.

At the acute stage of cerebral ischemia, treatment with IV recombinant tissue plasminogen activator (rtPA) is recommended worldwide[1–3]: it increases survival without dependency in patients treated within 4.5 hours of the onset of symptoms,[4–7] even in elderly participants.[8,9] At least 10% of stroke patients have preexisting dementia,[10] and even more in elderly patients and in patients with recurrent strokes.[10,11] Patients with prestroke cognitive impairment (PSCI) frequently have vascular lesions, such as cerebral amyloid angiopathy and hypertensive deep perforating vasculopathy, and brain lesions, such as white matter changes and microbleeds.[10–14] All these pathologic changes are associated with an increased risk of cerebral hemorrhage.[15,16]

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Patients with PSCI might also be more sensitive to the neurotoxic effects of rtPA on the ischemic brain tissue.[17–19] However, none of the previously reported observational studies has shown a clear association between PSCI and the risk of symptomatic intracerebral hemorrhage (sICH) after treatment with rtPA.[20–22] However, these studies were limited by their small sample size, the lack of systematic search for PSCI, the absence of important predictors of outcome in the analysis, and the lack of evaluation at 3 months.[20–22] In our previous retrospective study, in which most of these limitations were solved,[23] we found no difference in outcome after IV rtPA treatment between patients with and without PSCI, but patients were highly selected and accounted for less than 20% of all patients treated with IV rtPA.[23] To determine whether rtPA is safe and effective in ischemic stroke patients with PSCI would need a randomized placebo-controlled trial. Such a trial would not be ethical in the absence of evidence that rtPA is unsafe in patients with PSCI. The aim of this multicenter study was to evaluate the influence of PSCI on the clinical outcome of consecutive stroke patients treated with IV rtPA.

METHODS

Setting. We prospectively included all patients who were treated with IV rtPA for an acute cerebral ischemia in participating centers. The French part of OPHELIE-COG was conducted in the framework of the Strokavenir network, supported by the French Ministry of Health. The Japanese part of OPHELIE-COG was conducted in the 7 hospitals participating in the Fukuoka Stroke Registry[24] and in the Kawasaki Medical School Hospital. Centers became active between January 2012 and March 2013, and the last follow-up visit was on July 30, 2013.

Standard protocol approvals, registrations, and patient consents. OPHELIE-COG was an observational multicenter study conducted in French and Japanese centers. It recruited adults of both sexes who were treated with IV rtPA for cerebral ischemia and gave informed consent themselves or via a close relative. The study was approved by health authorities in both countries and by relevant ethical committees: Comité de Protection des Personnes (CPP) Nord Ouest IV Lille, France, by March 9, 2010, under registration number 10.677, and ethical committee of Kyushu Medical Center, Japan, by November 16, 2011, under registration number 11–75. We were not allowed to record in the database the ethnicity by French health authorities. OPHELIE-COG is registered under ClinicalTrials.gov identifier no. NCT01713491.

General management. French patients were treated according to the revised recommendations of the European Stroke Organisation, in which the time window for IV rtPA was extended up to 4.5 hours after onset.[1] Japanese patients were treated according to the Japanese guidelines[25] for IV rtPA therapy, which mainly differ from European ones by the dose of rtPA (Japan: 0.6 mg/kg body weight, maximum 60 mg; Europe: 0.9 mg/kg body weight, maximum 90 mg). The time window was extended to 4.5 hours on September 1, 2012, in Japan.[2]

Inclusion and exclusion criteria. All consecutive patients who were treated with IV rtPA in participating centers during the study period and consented for participation were eligible. Age over 80 years was not regarded as an exclusion criterion. Exclusion criteria were (1) an acute ischemic stroke sparing the middle cerebral artery territory; (2) thrombolytic therapy administered intra-arterially or combined with thrombectomy; (3) impairment of daily living before stroke onset with a prestroke modified Rankin Scale[26] score (mRS) $\geq$2; and (4) impossibility to perform the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) within 48 hours after admission, except when the patient had been diagnosed as cognitively impaired by a specialist (e.g., neurologist, psychiatrist, or geriatrician) before stroke onset, or classified as cognitively normal because of a score of 30 at discharge on the Mini-Mental State Examination (MMSE).[27]

Clinical assessment. The severity of the neurologic deficit at admission was evaluated by the NIH Stroke Scale (NIHSS).[4] The preexisting level of independence and functional outcome at 3 months after stroke onset were evaluated by the mRS.[26] When a face-to-face visit was not possible 3 months after stroke, the functional outcome was evaluated by a telephone survey with the patient, the family, or the treating physician.[28] Stroke subtypes were classified according to the criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study.[29] The evaluation of the preexisting cognitive status was assessed within 48 hours after stroke onset by French[30] or Japanese[31] translations of the short version of the IQCODE. This questionnaire consists of 16 questions regarding the changes observed in patients over the last 10 years in aspects of daily behavior requiring memory and other intellectual abilities. A close relative needs to be interviewed. Each item is given a score of 1–5 (1 = much improved; 2 = a bit improved; 3 = not changed; 4 = a bit worse; 5 = much worse). The overall score is the sum of the scores of each item, ranging from 16 to 80. The informant should have known the patient for at least 10 years and meet him or her at least once a week. The questionnaire has good reproducibility.[32] In the community, there is a good correlation between MMSE and IQCODE scores.[30] We classified patients as (1) having PSCI when the mean IQCODE score was greater than 3 (i.e., total score >48); and (2) cognitively normal when the mean IQCODE score was 3 or less. The threshold of 3 was chosen to consider in the PSCI group all patients who had a change over the last 10 years in one question of the questionnaire, and to increase the sensitivity of the test for a diagnosis of very mild cognitive impairment.

Study outcomes. The primary endpoint was favorable functional outcome (mRS score 0–1) at the 3-month visit. Secondary endpoints were (1) sICH defined according to the European Cooperative Acute Stroke Study II criteria,[33] (2) mRS score 0–2 (absence of dependence) at 3 months, or (3) death at 3 months.

Sample size calculation. As available data on rtPA in patients with cognitive impairment were scarce when the study was initiated, an intermediate analysis was planned after inclusion of 500 patients who reached the 3-month follow-up, to reevaluate the sample size.

Table 1 Baseline characteristics according to prestroke cognitive status

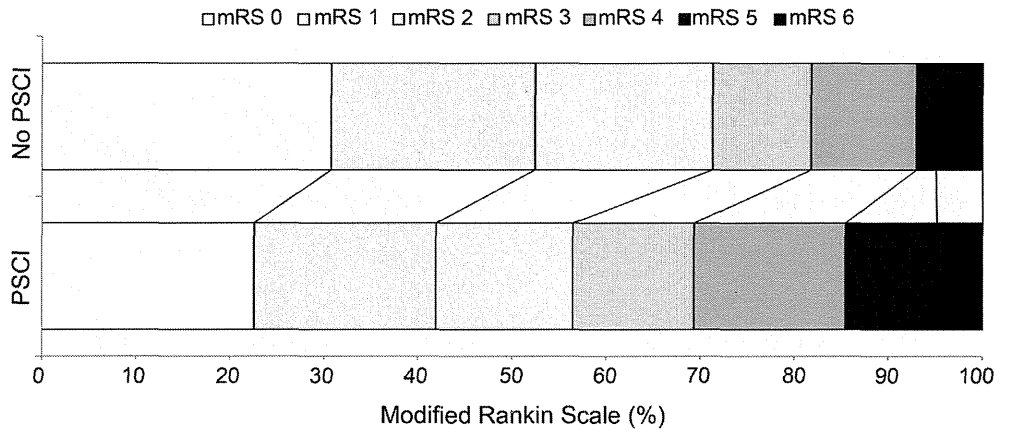
Demographic characteristics	With PSCI (n = 62)	Without PSCI (n = 143)	Unadjusted OR (95% CI)	p Value
Male	26 (41.9)	80 (55.9)	0.57 (0.31–1.04)	
Recruited in France	46 (74.2)	123 (86.0)	0.47 (0.22–0.98)[b]	
Age, y, median (IQR)[a]	77 (67–82)	66 (54–77)		<0.001[b]
Medical history				
Body weight, kg, median (IQR)[a]	71 (59–83)	74.4 (67.3–82.8)		0.087
Prestroke mRS = 0	50 (80.6)	135 (94.4)	0.25 (0.10–0.64)[b]	
Previous stroke	7 (11.3)	8 (5.6)	2.15 (0.74–6.21)	
Previous MI	6 (9.7)	24 (16.8)	0.53 (0.21–1.37)	
Atrial fibrillation	15 (24.2)	26 (18.2)	1.44 (0.70–2.95)	
Arterial hypertension	43 (69.4)	86 (60.1)	1.50 (0.79–2.83)	
Diabetes mellitus	10 (16.1)	24 (16.8)	0.95 (0.43–2.14)	
Smoking	11 (17.7)	46 (32.2)	0.45 (0.22–0.95)[b]	
Excessive alcohol consumption	4 (6.5)	15 (10.5)	0.59 (0.19–1.85)	
Ongoing anticoagulant therapy	5 (8.1)	9 (6.3)	1.31 (0.42–4.07)	
Ongoing antiplatelet therapy	20 (32.3)	29 (20.3)	1.87 (0.96–3.66)	
IQCODE score, median (IQR)[a]	3.25 (3.22–3.38)	3.00 (2.88–3.00)		<0.0001[b]
Presumed cause				
Large-artery atherosclerosis	7 (11.3)	30 (21)	0.48 (0.20–1.16)	
Cardioembolism	25 (40.3)	52 (36.4)	1.18 (0.64–2.18)	
Small-vessel occlusion	3 (4.8)	5 (3.5)	1.40 (0.32–6.06)	
Other definite causes	1 (1.6)	6 (4.2)	0.37 (0.04–3.18)	
Unknown causes	26 (35)	50 (35.0)	1.34 (0.73–2.47)	
Characteristics of thrombolysis				
Systolic BP before rtPA, mm Hg, median (IQR)[a]	156 (141–161)	150 (135–162)		0.166
INR >1.6	0 (0.0)	3 (2.1)	NA	
NIHSS score before rtPA, median (IQR)[a]	9 (5–17)	8 (6–16)		0.671
Serum glucose level, mg/dL, median (IQR)[a]	1.12 (1.00–1.40)	1.18 (1.04–1.40)		0.449
Platelets, 1,000/mm^3, median (IQR)[a]	219 (189–262)	231 (190–273)		0.348
Onset-to-needle time, min, median (IQR)[a]	109 (97–116)	170 (126–184)		0.117

Abbreviations: BP = blood pressure; CI = confidence interval; INR = international normalized ratio; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; IQR = interquartile range; MI = myocardial infarction; mRS = modified Rankin Scale; NA = not assessable; NIHSS = NIH Stroke Scale; OR = odds ratio; PSCI = prestroke cognitive impairment; rtPA = recombinant tissue plasminogen activator.
Values are number of patients (%) unless specified, with unadjusted OR and 95% CI.
[a] Median values (IQR) with Mann-Whitney *U* test. ORs >1 mean that the variable is more frequent in patients with PSCI.
[b] Significant difference.

While the OPHELIE-COG study was running, we retrospectively analzyed the data that became available in patients who had been treated with IV rtPA before inclusion in either Biostroke (NCT00763217) or Strokdem (NCT01330160), 2 studies of biomarkers conducted in the stroke unit of the Lille University Hospital. Although patients included in these studies were highly selected and the sample size was limited, this analysis showed that the chance to detect a significant difference between patients with and without PSCI would be small,[23] and it was therefore decided to anticipate the intermediate analysis of OPHELIE-COG and to analyze available data. After this intermediate analysis, it was decided to stop OPHELIE-COG for futility.

Statistical analyses. We performed the statistical analysis with the SPSS 22.0 package for windows. We used median values, interquartile ranges (IQRs), and percentages. We used the Mann-Whitney *U* test to compare continuous variables. Probability values <0.05 were considered statistically significant. We compared groups for categorical variables with unadjusted odds ratio (ORs) with 95% confidence intervals (CIs). Adjusted ORs and 95% CIs for the study outcome were estimated by logistic regression analyses with the variables PSCI (classified 1 when present, 0 when absent), age (years), baseline NIHSS score (points), and onset-to-needle time (minutes) forced into the model. Finally, we performed a pooled analysis of the results of OPHELIE-COG and of the previously published joined analysis of Biostroke and Strokdem to test consistency of the results in different settings.[23] The primary research question was whether the outcome of patients treated by IV rtPA was influenced by the presence of PSCI to such an extent that the benefit of rtPA could be lost.

Figure 1 Outcome after 3 months evaluated by the modified Rankin Scale



Outcome in patients with and without prestroke cognitive impairment (PSCI), evaluated by the modified Rankin Scale (mRS) after 3 months, with 0 meaning total recovery and 6 meaning death ($p = 0.215$).

RESULTS We recruited 205 patients, including 106 men (51.7%), with a median age of 70 years (IQR 56–80) and a median NIHSS score of 8 (IQR 5–16). The 169 patients (82.4%) recruited in France were younger than those recruited in Japan: median age 69 years (IQR 56–78) vs 77 years (IQR 61–85) ($p = 0.03$). Sixty-two patients (30.2%) met criteria for PSCI.

The baseline characteristics of patients with and without PSCI are compared in table 1: patients with PSCI were significantly older and more likely to have mRS 1 prior to stroke than those without.

The whole range of mRS scores 3 months after stroke is detailed in figure 1. Although patients with PSCI had more sICH and were less frequently independent 3 months after stroke than those without, they did not differ for any of the 4 outcome measures after adjustment for age, baseline NIHSS score, and onset-to-needle time (table 2).

The pooled analysis of patients included in OPHELIE-COG and in the Biostroke/Strokdem study found no significant association of PSCI with any of the 4 endpoints, despite a small tendency toward a lower frequency of mRS 0–1/0–2 after 3 months and a slightly lower mortality in patients with PSCI (figure 2). The risk of being dependent (mRS 3–5) after 3 months was not significantly increased in patients with PSCI after adjustment for age, baseline NIHSS, and onset-to-needle time.

DISCUSSION Our study has shown that, although patients with PSCI had more sICH and were less frequently independent 3 months after stroke than those without, they did not differ for any of the 4 outcome measures after adjustment for age, baseline NIHSS score, and onset-to-needle time. Therefore, the small differences in outcomes are the consequence of differences in case mix. This study provides Class IV evidence that in patients with PSCI presenting with acute ischemic stroke, IV rtPA improves outcomes.

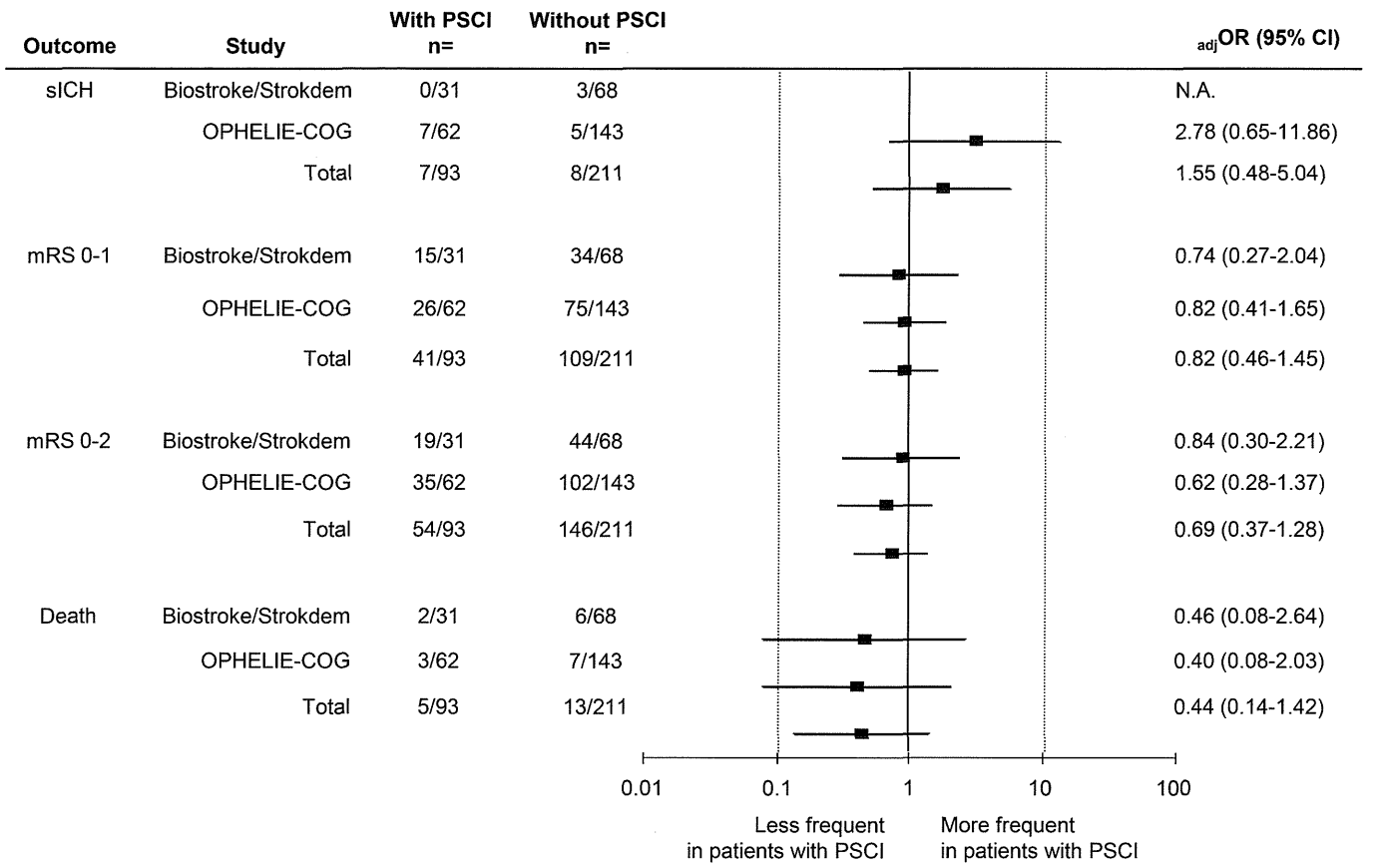
The strengths of OPHELIE-COG are the prospective design, the standardized evaluation of the preexisting cognitive status, and the multicenter,

Table 2 Clinical outcomes according to prestroke cognitive status

	With PSCI (n = 62), n (%)	Without PSCI (n = 143), n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Outcome				
sICH (ECASS II)	7 (11.3)	5 (3.5)	3.50 (1.06-11.54)[b]	2.78 (0.65-11.86)
mRS 0-1 at 3 months	26 (41.9)	75 (52.4)	0.65 (0.36-1.20)	0.82 (0.41-1.65)
mRS 0-2 at 3 months	35 (56.5)	102 (71.3)	0.52 (0.28-0.97)[b]	0.62 (0.28-1.37)
Death at 3 months	3 (4.8)	7 (4.9)	0.99 (0.25-3.95)	0.40 (0.08-2.03)

Abbreviations: CI = confidence interval; ECASS II = European Cooperative Acute Stroke Study II; mRS = modified Rankin Scale; OR = odds ratio; PSCI = prestroke cognitive impairment; sICH = symptomatic intracerebral hemorrhage.
ORs >1 mean that the variable is more frequent in patients with PSCI.
[a] Adjusted for baseline NIH Stroke Scale score, age, and onset-to-needle time.
[b] Significant difference.

Figure 2 Pooled analysis of OPHELIE-COG, Biostroke, and Strokdem



Adjusted odds ratios ($_{adj}$OR) and 95% confidence intervals (CI) for the outcomes at 3 months in patients with and without prestroke cognitive impairment (PSCI). The ORs are adjusted for age, baseline NIH Stroke Scale score, and onset-to-needle time. mRS = modified Rankin Scale; NA = not assessable; sICH = symptomatic intracerebral hemorrhage.

binational, and multiethnic recruitment. To our knowledge, there was until now no study that prospectively and systematically evaluated the safety of IV rtPA in cognitively impaired patients consecutively admitted for cerebral ischemia. The use of a standardized and validated questionnaire was of major importance, because the preexisting cognitive status could not be directly evaluated by usual neuropsychological tests, because of the influence of the stroke lesion. Up to now, the IQCODE is the most appropriate test to evaluate the preexisting cognitive status.[10] Besides, the results of OPHELIE-COG are in line with those of our retrospective analysis of highly selected patients recruited in the Strokdem and Biostroke studies.[23]

The main limitation of OPHELIE-COG is that this study mainly provides safety information and no direct evidence of the efficacy of rtPA in patients with PSCI in the absence of a control group and randomization. Heterogeneity in the dose of rtPA between Europe and Japan has no reason to have influenced the results, as suggested by a Japanese postmarketing survey showing a proportion of favorable outcomes at 3 months of 39%,[34] i.e., very close to that found in the European registry.[35,36] The absence of patients with major PSCI, because of the exclusion of patients with a prestroke mRS of 2 or more, does not allow any conclusion for patients with severe cognitive impairment. As the baseline severity of the study population was slightly lower than those in trials and in most observational cohorts, with a median NIHSS score of 8,[37] OPHELIE-COG does not allow any conclusion for severe strokes. Therefore, OPHELIE-COG provides interesting conclusions that are valid only for patients with mild cognitive impairment and ischemic stroke of moderate severity. We could not adjust for ethnicity because the French regulation does not allow inclusion of ethnicity in a database in the absence of a strong rationale.

As PSCI was evaluated retrospectively at admission, we could not differentiate vascular, degenerative, and mixed causes, and therefore we included both pathologies in the same group, although efficacy and safety of rtPA may differ between vascular and degenerative PSCI.

OPHELIE-COG provides another piece of evidence that patients with mild cognitive impairment

before stroke should receive rtPA if they are otherwise eligible. This conclusion cannot be extended to patients with severe cognitive impairment or to patients with severe strokes.

AUTHOR CONTRIBUTIONS

Kei Murao analyzed and interpreted all data, performed the literature search, and drafted the manuscript. Didier Leys conceptualized the study, analyzed, interpreted, and collected data, and drafted the manuscript. Agnès Jacquin interpreted study data and revised the manuscript. Takanari Kitazono conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Régis Bordet conceptualized the study, interpreted data, and revised the manuscript. Yannick Béjot conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Kazumi Kimura conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Olivier Godefroy conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Yoshinobu Wakisaka conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Solène Moulin interpreted study data and revised the manuscript. Tetsuro Ago collected and interpreted study data and revised the manuscript. Igor Sibon conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Stéphanie Bombois interpreted study data and revised the manuscript. Jean-Louis Mas conceptualized and designed the study, interpreted study data, and revised the manuscript. Hilde Hénon conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Florence Pasquier interpreted study data and revised the manuscript. Maurice Giroud conceptualized and designed the study, interpreted and collected study data, and revised the manuscript. Charlotte Cordonnier interpreted study data and revised the manuscript. Yasushi Okada conceptualized and designed the study, interpreted and collected study data, and revised the manuscript.

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DISCLOSURE

K. Murao reports no disclosures relevant to the manuscript. D. Leys had partnership with Boehringer-Ingelheim for trials, speaker at symposia and advisory board meetings, and fees paid toward research at Association pour le Développement de la Recherche et de l'Innovation dans le Nord-Pas de Calais (ADRINORD). A. Jacquin reports no disclosures relevant to the manuscript. T. Kitazono had partnership with Mitsubishi Tanabe Pharma Corporation for trials. R. Bordet reports no disclosures relevant to the manuscript. Y. Béjot served as a member of a scientific committee for Boehringer-Ingelheim France. K. Kimura reports no disclosures relevant to the manuscript. O. Godefroy had partnership with Novartis for trials, speaker at symposia and advisory board meetings. Y. Wakisaka, S. Moulin, T. Ago, I. Sibon, and S. Bombois report no disclosures relevant to the manuscript. J. Mas had partnership with Boehringer-Ingelheim for trials, speaker at symposia and advisory board meetings. H. Hénon had partnership with Boehringer-Ingelheim for trials, fees paid toward research at ADRINORD. F. Pasquier and M. Giroud report no disclosures relevant to the manuscript. C. Cordonnier had partnership with Boehringer-Ingelheim for trials and speaker at symposia, fees paid toward research at ADRINORD. Y. Okada reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Regular Article

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

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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

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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.

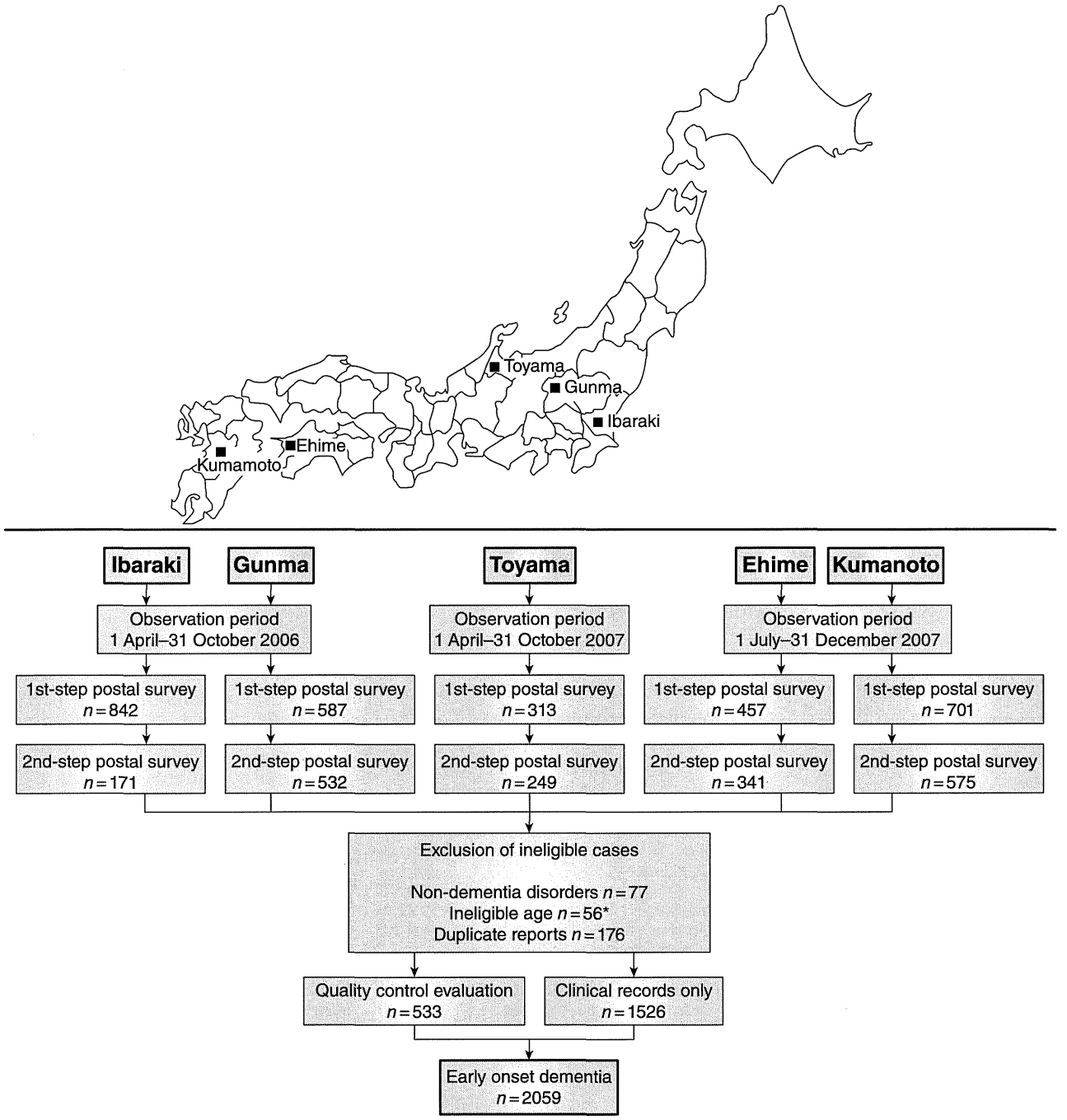

Figure 1. Map of Japan and schedule of each catchment area's survey.

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

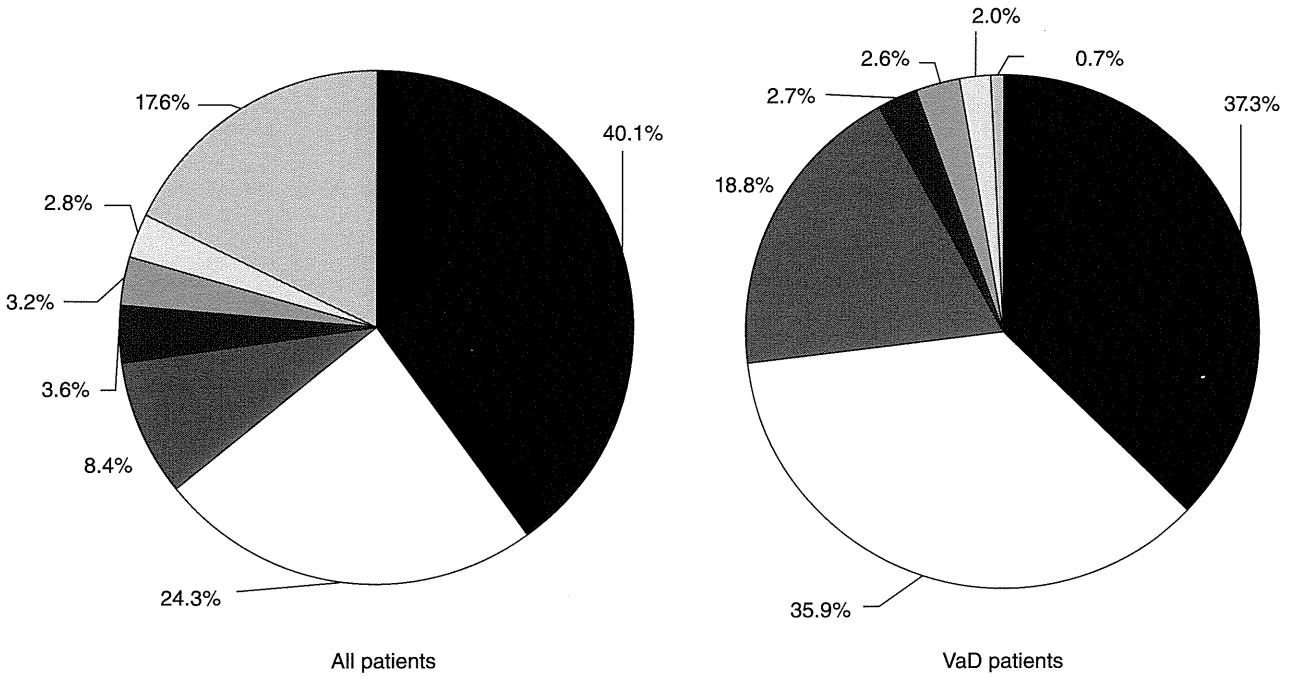

Figure 2. Distribution of diagnoses. All patients: (■) vascular dementia (VaD); (□) Alzheimer's disease; (■) Head trauma; (■) frontotemporal lobar degeneration; (■) alcohol-related dementia; (□) dementia with Lewy bodies/Parkinson's disease with dementia; and (□) Others. VaD patients: (■) Large cortical 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.

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PLOS ONE

Consumption of Green Tea, but Not Black Tea or Coffee, Is Associated with Reduced Risk of Cognitive Decline

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Abstract

Our objective was to determine whether the consumption of green tea, coffee, or black tea influences the incidence of dementia and mild cognitive impairment (MCI) in older people. We conducted a population-based prospective study with Japanese residents aged >60 years from Nakajima, Japan (the Nakajima Project). Participants received an evaluation of cognitive function and blood tests. The consumption of green tea, coffee, and black tea was also evaluated at baseline. Of 723 participants with normal cognitive function at a baseline survey (2007–2008), 490 completed the follow up survey in 2011–2013. The incidence of dementia during the follow-up period (mean ± SD: 4.9±0.9 years) was 5.3%, and that of MCI was 13.1%. The multiple-adjusted odds ratio for the incidence of overall cognitive decline (dementia or MCI) was 0.32 (95% CI: 0.16–0.64) among individuals who consumed green tea every day and 0.47 (95% CI: 0.25–0.86) among those who consumed green tea 1–6 days per week compared with individuals who did not consume green tea at all. The multiple-adjusted odds ratio for the incidence of dementia was 0.26 (95% CI: 0.06–1.06) among individuals who consumed green tea every day compared with those who did not consume green tea at all. No association was found between coffee or black tea consumption and the incidence of dementia or MCI. Our results indicate that green tea consumption is significantly associated with reduced risk of cognitive decline, even after adjustment for possible confounding factors.

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Introduction

Coffee and tea are widely consumed around the world. In Japan and other Asian countries, green tea is a popular beverage, whereas in the Western countries, black tea is popular. Coffee, tea and tea-related polyphenols have been extensively studied for their neuroprotective effects and their potential for preventing neurodegenerative diseases, including Alzheimer's disease (AD) [1–7]. Coffee and tea contain large amounts of caffeine, which has been investigated for its neuroprotective effects both *in vivo* and *in vitro* [8,9]. However, evidence from cohort studies that examine the relationship between green tea or coffee consumption and dementia is limited and inconsistent.

Several longitudinal studies [10–13] have investigated the relationship between coffee consumption and dementia, AD, or cognitive decline, but findings from these studies are also inconsistent. In addition, longitudinal studies of black tea consumption have not found any association with reduced risks for dementia, AD, or cognitive decline [14,15]. One cross-sectional study has shown that higher green tea consumption is associated with lower prevalence of cognitive impairment [16].

We hypothesized that the consumption of beverages rich in polyphenols and caffeine, such as green tea, coffee, or black tea, would be protective and would delay the onset of dementias including AD. In the present longitudinal study, we aimed to determine whether the consumption of the aforementioned beverages is associated with the incidence of dementia and mild cognitive impairment (MCI) in the general population.

Methods

Study participants

The Nakajima Project was a population-based cohort study that investigated correlations between lifestyle and the prevalence of dementia in elderly Japanese individuals. The study was conducted in Nakajima, in the Nanao district of Ishikawa Prefecture, Japan. The study design was described previously [17,18].

Participants were recruited as a part of the Nakajima Project. The baseline survey was conducted between 2007 and 2008. On April 1, 2007, 2,845 people who were 60 years or older were legally residing in Nakajima. These elderly residents were eligible