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Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study

Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, Arima H, Sasaki K, Iida M, Iwaki T, Kanba S, Kiyohara Y. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese community: the Hisayama Study.

Objective: To examine secular trends in the prevalence of Alzheimer's disease (AD) and vascular dementia (VD) in a general Japanese population.
Method: Four cross-sectional examinations were conducted among residents of a Japanese community aged ≥65 in 1985, 1992, 1998 and 2005.
Results: The age- and sex-adjusted prevalence of all-cause dementia significantly increased with time (6.0% in 1985, 4.4% in 1992, 5.3% in 1998 and 8.3% in 2005; *P* for trend = 0.002). A similar trend was observed for AD (1.1%, 1.3%, 2.3% and 3.8% respectively; *P* for trend < 0.001), while the age- and sex-adjusted prevalence of VD and other/unclassified dementia showed J-shaped patterns (for VD: 2.3%, 1.5%, 1.5% and 2.5%, respectively, *P* for trend = 0.82; for other/unclassified dementia: 2.6%, 1.7%, 1.5% and 2.0%, *P* for trend = 0.26). The prevalence of AD was likely to increase with time from 1985 to 2005 among subjects aged 75 or older. The ratio of the prevalence of VD to that of AD decreased with time (2.1 in 1985, 1.2 in 1992, 0.7 in 1998 and 0.7 in 2005).
Conclusion: Our findings suggest that the prevalence of all-cause dementia and AD significantly increased over the past two decades in the general Japanese population.

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Key words: dementia; Alzheimer's disease; vascular dementia; prevalence; secular trend

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Significant outcomes

- The prevalence of all-cause dementia significantly increased over the past 20 years in a general population of Japanese elderly.
- The prevalence of Alzheimer's disease in 2005 was approximately threefold higher than that in 1985.
- The ratio of the prevalence of vascular dementia to that of Alzheimer's disease decreased with time.

Limitations

- The diagnosis of dementia and its types was made based only on clinical findings.
- There was a variation in participation rate among the four cross-sectional examinations.
- We have no information regarding factors that contributed to trends in the prevalence of dementia.

Introduction

Approximately 24.3 million people suffer from dementia globally, and this number is expected to double every 20 years to 81.1 million by 2040 because of the rapid increase in the number of the elderly worldwide (1). In Japan, where the elderly population has been increasing faster than in other

countries and the ratio of the elderly to the total population has become the highest in the world, dementia has become a serious social, medical and economic problem. Effective prevention requires a strategy based on information about the morbidity of dementia and its subtypes and its secular trends in general populations. A number of studies have investigated the prevalence of dementia and its subtypes in various populations worldwide (2–8). However, only a few population-based studies have investigated secular trends in the prevalence of dementia in defined populations (9–14), and there were very few studies examining these trends in the 2000s.

Aims of the study

The aim of this analysis was to investigate secular trends in the prevalence of all-cause dementia and dementia subtypes over the past two decades in a general population of Japanese elderly.

Material and methods

Study population

The Hisayama Study is a prospective cohort study of cerebro-cardiovascular diseases in a subrural community, the town of Hisayama, which is adjacent to the metropolitan area of Fukuoka, Japan. The population of the town has distributions of age, occupational status and nutrient intake that are almost identical with those for the whole of Japan (15). The population of the town has been stable for 50 years. As a part of the study, four cross-sectional examinations of dementia have been conducted on Hisayama residents aged 65 or older (10, 16, 17). In 1985, a total of 938 residents in that age group were invited to participate in a cross-sectional examination of dementia. After exclusion of 26 subjects who died, 10 who moved out of the town before the examination and 15 who refused the examination, 887 subjects (353 men and 534 women) underwent the examination (participation rate 94.6%) (Table 1). In a similar manner, we examined 1189 subjects (475 men and 714 women) among 1231 residents (participation rate 96.6%) in 1992, 1437 subjects (571 men and 866 women) among 1442 residents (participation rate 99.7%) in 1998 and 1566 subjects (612 men and 954 women) among 1711 residents (participation rate 91.5%) in 2005. The number of elderly subjects increased during the study period because of aging of the population, which was consistent with the national trend.

Table 1. Demographic characteristics of subjects and diagnostic procedures of dementia in each examination

	Year of examination			
	1985 (n = 887)	1992 (n = 1189)	1998 (n = 1437)	2005 (n = 1566)
Age, years	73.7 ± 6.4	74.2 ± 6.9	74.8 ± 7.2	75.9 ± 7.4
Women, %	60.2	60.1	60.3	60.9
Participation rate, %	94.6	96.6	99.7	91.5
Neuropsychological test	HDS	HDS HDS-R MMSE	HDS-R	HDS-R MMSE
Diagnosis of dementia	DSM-III	DSM-III-R	DSM-III-R	DSM-III-R

HDS, Hasegawa's Dementia Rating Scale; HDS-R, HDS, revised version; MMSE, Mini-Mental State Examination; DSM-III, Diagnostic and Statistical Manual of Mental Disorders, third edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, revised third edition.

Survey of dementia

We carried out a two-phase survey of dementia at each examination. The first screening survey included neuropsychological tests [Hasegawa's Dementia Scale (HDS) (18) in 1985; HDS, HDS revised version (HDS-R) (19) and Mini-Mental State Examination (MMSE) (20) in 1992; HDS-R in 1998; and HDS-R and MMSE in 2005] and questionnaires regarding psychological and medical symptoms, medical conditions and activities of daily living (Table 1). HDS and HDS-R are neuropsychological tests that are widely utilized in Japan and comprised of questions regarding orientation, memory function, common knowledge and calculation capacities. We confirmed the excellent agreement among these tests in 1992 (agreement rate = 95% and kappa coefficient = 0.77 between MMSE and HDS; agreement rate = 96% and kappa coefficient = 0.81 between MMSE and HDS-R). The assessment of neuropsychological tests was performed by investigators who were trained in advance in the use of the tests. For subjects whose test scores were below the cutoff points (22/32.5 for HDS, 21/30 for HDS-R and MMSE), comprehensive investigations, including interviews of the families or attending physicians, physical and neurological examinations and a review of the clinical records, were conducted.

Diagnosis of dementia

The diagnosis of dementia was made clinically based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) (21) in 1985 and those of the DSM-III revised version (DSM-III-R) (22) in 1992, 1998 and 2005 by trained neurologists/psychia-

trists who were supervised by a single neurologist (Y.K.) over the study period (Table 1). We used Karasawa's criteria (23) for the clinical evaluation of dementia as supplementation. The latter has been widely used for epidemiological research on dementia in Japan and divides cases with dementia into four grades of severity according to loss of intellectual abilities, severity of interference with social and occupational functioning and inability to care for oneself. The ischemic score of Hachinski et al. (24) was also used to differentiate vascular dementia (VD) from Alzheimer's disease (AD).

Among a total of 887 subjects screened in 1985, 114 (12.9%) underwent the secondary comprehensive investigation, and of those, 59 (6.7%) were diagnosed as having dementia. Similarly, 194 subjects (16.3%) in 1992, 258 (18.0%) in 1998 and 395 (25.2%) in 2005 underwent comprehensive investigations, and of those, 68 (5.7%), 102 (7.1%) and 195 (12.5%), respectively, were diagnosed as having dementia.

Statistical analysis

Adjusted prevalence of dementia was estimated with 95% confidence interval (CI) by the direct method with 5-year age groupings, where the total population in Japan at the time of the initial examination was used as a standard population. Differences in the adjusted prevalence of dementia were tested, and the adjusted odds ratio (OR) and 95% CI were estimated using the logistic regression model including age taken as a continuous variable and sex.

Ethical considerations

The study protocol was approved by the Human Ethics Review Committee of the Graduate School of Medical Sciences, Kyushu University.

Results

Demographic characteristics of the subjects in the examinations conducted in 1985, 1992, 1998 and 2005 are shown in Table 1. The mean age was slightly increased from 73.7 years in 1985 to 75.9 years in 2005. Women accounted for approximately 60% of total subjects over the four examinations.

The prevalence of all-cause dementia in the four examinations is shown in Table 2. The age- and sex-adjusted prevalence of all-cause dementia significantly increased from 6.0% in 1985 to 8.3% in 2005 (P for trend = 0.002) and was 1.34-fold (P = 0.08) higher in 2005 than in 1985. This trend was observed in the age- and sex-adjusted prevalence of all-cause dementia for both sexes but was only significant for women (P for trend = 0.007).

Table 3 shows the secular trends in the prevalence of dementia by subtypes. The age- and sex-adjusted prevalence of AD significantly increased from 1.1% in 1985 to 3.8% in 2005 (P for trend <0.001) and was 2.00-fold higher in 1998 (P = 0.04) and 3.28-fold higher in 2005 ($P < 0.001$) than in 1985. The age- and sex-adjusted prevalence of VD showed a decreasing trend between 1985 and 1998 (from 2.3% to 1.5%) and then an increasing trend to 2.5% in 2005. A similar trend

Table 2. Secular trends in prevalence of all-cause dementia from 1985 to 2005

	Year of examination				
	1985	1992	1998	2005	P for trend
Total					
Population at risk	887	1189	1437	1566	0.002
No. of cases of dementia	59	68	102	195	
Crude prevalence (%) (95% CI)	6.7 (5.0–8.3)	5.7 (4.4–7.1)	7.1 (5.7–8.5)	12.5 (10.7–14.2)	
Age- and sex-adjusted prevalence (%) (95% CI)	6.0 (4.4–7.6)	4.4 (3.3–5.6)	5.3 (4.2–6.4)	8.3 (7.0–9.5)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.70 (0.48–1.03)	0.78 (0.55–1.12)	1.34 (0.97–1.87)	
Women					
Population at risk	534	714	866	954	0.007
No. of cases of dementia	40	51	77	141	
Crude prevalence (%)(95% CI)	7.5 (5.2–9.8)	7.1 (5.2–9.1)	8.9 (6.9–10.9)	14.8 (12.3–17.2)	
Age-adjusted prevalence (%) (95% CI)	6.6 (4.5–8.6)	5.3 (3.8–6.8)	6.4 (4.9–7.9)	9.3 (7.7–10.9)	
Age-adjusted odds ratio (95% CI)	1 (reference)	0.73 (0.46–1.17)	0.83 (0.54–1.29)	1.39 (0.93–2.10)	
Men					
Population at risk	353	475	571	612	0.13
No. of cases of dementia	19	17	25	54	
Crude prevalence (%) (95% CI)	5.4 (3.0–7.8)	3.6 (1.9–5.3)	4.4 (2.7–6.1)	8.8 (6.5–11.2)	
Age- adjusted prevalence (%) (95% CI)	5.4 (3.0–7.8)	3.6 (1.9–5.3)	4.2 (2.6–5.9)	7.2 (5.3–9.2)	
Age-adjusted odds ratio (95% CI)	1 (reference)	0.63 (0.32–1.25)	0.67 (0.36–1.27)	1.25 (0.71–2.20)	

95% CI: 95% confidence interval.

Table 3. Secular trends in prevalence of dementia subtypes from 1985 to 2005

	Year of examination				
	1985 (n = 887)	1992 (n = 1189)	1998 (n = 1437)	2005 (n = 1566)	P for trend
Alzheimer's disease					
No. of cases of dementia	12	21	49	96	<0.001
Crude prevalence (%) (95% CI)	1.4 (0.6–2.1)	1.8 (1.0–2.5)	3.4 (2.5–4.4)	6.1 (4.9–7.4)	
Age- and sex-adjusted prevalence (%) (95% CI)	1.1 (0.4–1.7)	1.3 (0.7–1.9)	2.3 (1.6–3.0)	3.8 (3.0–4.6)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	1.11 (0.53–2.32)	2.00* (1.04–3.87)	3.28** (1.75–6.14)	
Vascular dementia					
No. of cases of dementia	21	22	25	51	0.82
Crude prevalence (%) (95% CI)	2.4 (1.4–3.4)	1.9 (1.1–2.6)	1.7 (1.1–2.4)	3.3 (2.4–4.2)	
Age- and sex-adjusted prevalence (%) (95% CI)	2.3 (1.3–3.3)	1.5 (0.8–2.2)	1.5 (0.9–2.1)	2.5 (1.7–3.2)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.70 (0.38–1.29)	0.58 (0.32–1.06)	0.95 (0.56–1.62)	
Other/unclassified dementia					
No. of cases of dementia	26	25	28	48	0.26
Crude prevalence (%) (95% CI)	2.9 (1.8–4.1)	2.1 (1.3–2.9)	1.9 (1.2–2.7)	3.1 (2.2–3.9)	
Age- and sex-adjusted prevalence (%) (95% CI)	2.6 (1.6–3.7)	1.7 (1.0–2.4)	1.5 (0.9–2.2)	2.0 (1.4–2.7)	
Age- and sex-adjusted odds ratio (95% CI)	1 (reference)	0.61 (0.35–1.08)	0.50 (0.29–0.87)	0.69 (0.41–1.14)	

95% CI: 95% confidence interval; *P < 0.05, **P < 0.01 vs. 1985.

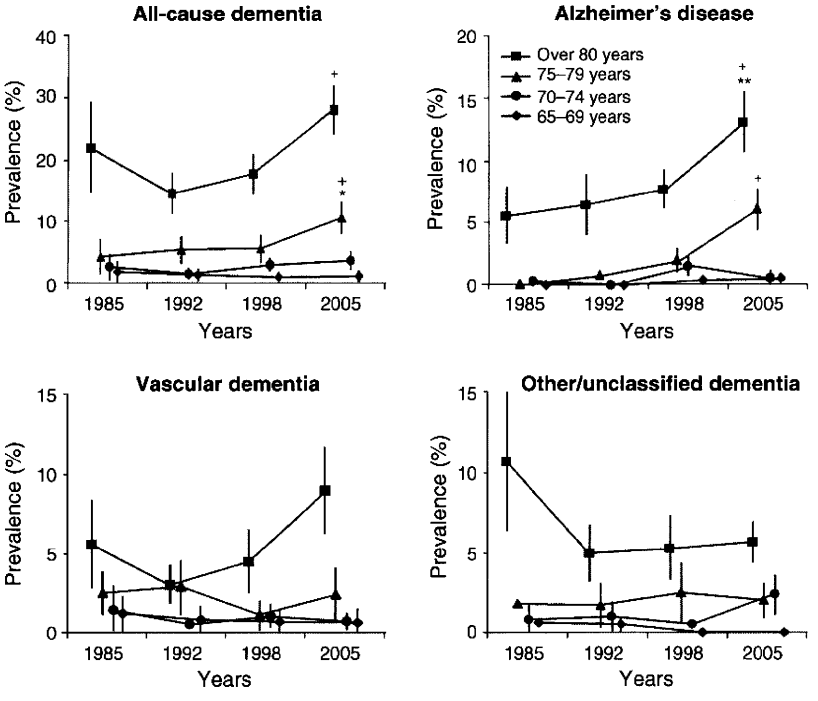

Fig. 1. Secular trends in sex-adjusted prevalence of dementia and its subtypes according to age groups. *P < 0.05, **P < 0.01 vs. 1985, +P for trend < 0.01. The vertical bars of 95% confidence intervals of adjusted prevalence were truncated at zero or more.

was observed for other/unclassified dementia. As a result, the ratio of the prevalence of VD to that of AD decreased with time (2.1 in 1985, 1.2 in 1992, 0.7 in 1998 and 0.7 in 2005).

Figure 1 shows the secular trends in the sex-adjusted prevalence of all-cause dementia and its subtypes according to age groups. The prevalence of all-cause dementia significantly increased from 1985 to 2005 among subjects aged 75 or older (P for trend < 0.01). Such a trend was also observed for the prevalence of AD in the same age group (P for trend < 0.01). The prevalence of VD tended to increase among subjects aged 80 or older in recent years (P for trend = 0.06). There were no clear changes in the prevalence of others/unclassified dementia.

Discussion

The present analysis of repeated cross-sectional examinations in a general population of Japanese elderly demonstrated that the prevalence of all-cause dementia significantly increased from 1985 to 2005. A similar trend was observed for AD but not

for VD. The prevalence of all-cause dementia and AD increased with time among subjects aged 75 or older, while increasing prevalence of VD was observed among subjects aged 80 or older.

Several population-based observational studies have reported secular trends in the prevalence of dementia (9–14). The Lundby Study conducted repeated cross-sectional examinations of dementia in a Swedish community and found no significant changes in the prevalence of senile dementia and multi-infarct dementia from 1945–1957 to 1957–1972 (9). The ZARADEMP project has also found no clear difference in the prevalence of dementia in a Southern European population in 1988–1989 and the prevalence in 1994–1996 (13). In contrast, an observational study from Rochester, Minnesota, in the USA demonstrated that the prevalence of dementia and AD significantly increased from 1975 to 1985 (11). An observational study from Beijing, China, also reported that the prevalence of dementia was slightly higher in 1997 than in 1986 and that AD increased its ranking from the second most common type of dementia (1986) to the most common type (1997) (12). An epidemiological study in the town of Daisen, Japan, has also demonstrated that the prevalence of all-cause dementia, AD and VD increased from 1980 to 2000 (14). In the present study, the prevalence of all-cause dementia and AD increased from 1985 to 2005 in a Japanese community. Although results obtained from Western countries were inconclusive, there may be an increasing burden of dementia in Asian countries.

The ratio of the prevalence of VD to that of AD has been shown to be an effective index for comparing the prevalence of VD and AD in various regions (3). In their recent review, Suh and Shah (3) used this ratio to compare the prevalence of VD and AD in numerous countries and found that AD was more prevalent than VD in USA and Europe. On the other hand, in Asian countries (China, Korea and Japan), there has been a temporal change in the VD/AD ratio. Although VD was more prevalent than AD in Asian countries before 1989, AD has become nearly twice as prevalent as VD since early 1990s (3). The present study confirms the findings of previous observational studies and suggests that AD has become more prevalent than VD in the Asian region in recent years.

The causes of the increase in the prevalence of all-cause dementia and AD observed in our study were not completely resolved. Aging of the study population may be a probable cause of these findings, because age is one of the strongest risk factors for cognitive decline (16, 25). However, the increasing trends in the prevalence of dementia remained significant even after controlling for the confounding effects of age using two different statistical methods, i.e. the direct method using 5-year age groupings and the logistic regression model including age taken as a continuous covariate. Therefore, aging of the study population is not likely to be a leading cause for increasing prevalence of dementia. Another possible cause would be the recent increase in the prevalence of metabolic disorders, such as obesity, hypercholesterolemia and glucose intolerance (15), which have been associated with the risk of AD (26–33).

Another interesting finding of the present study is that the age- and sex-adjusted prevalence of VD decreased from 1985 to 1998 and then increased in 2005, although the trend was not significant. A J-shaped trend in VD was observed among subjects aged 80 or older. VD has not only been shown to be associated with metabolic disorders but also with hypertension. Therefore, the decline in the prevalence of VD in the 1990s may have been ascribable to an improvement in the management of hypertension. In fact, during this period, the incidence and mortality of stroke significantly decreased in Japan, especially among the elderly (34). Without doubt, the popularization of antihypertensive therapy greatly contributed to this welcome trend. However, the steep increase in metabolic disorders and partly insufficient control of hypertension, especially among the elderly, may be responsible for the increasing prevalence of VD in recent years.

In Japan, the number of elderly subjects who lived in old-age homes or were institutionalized in other medical care facilities increased during the study period along with the improvement in the national medical care system for the elderly. Thus, the increase in subjects with dementia in our study may have been attributable to more effective management of these patients in recent years. However, this influence was suggested to be limited because the increase in the prevalence was observed only for AD but not for VD and other/unclassified dementia, and the 10-year survival rates were not significantly different among dementia subtypes in Hisayama residents (17).

The strengths of our study include its long observational period, high participation rates and relatively consistent way to diagnose dementia. The study has three limitations. First, the diagnosis of dementia and its types was made based only on clinical findings. However, we used typical dementia – i.e., AD and VD – as target disease, and the prevalences of all-cause dementia, AD and VD were similar to those obtained from other

observational studies in Asian regions (5, 35–41). Therefore, we believe that this bias is not likely to invalidate the present findings. Second, there was a variation in participation rate among the four cross-sectional examinations. It is generally agreed that an acceptable participation rate in a population-based study, i.e., a rate that practically eliminates the threat of selection bias attributable to non-participants, is above 70% of the target population (42, 43). We enrolled more than 90% of residents in every examination, and, therefore, we believe that the findings of the present study reflect the actual secular trends in prevalence in the Japanese population. Third, we have no information regarding factors that contributed to trends in the prevalence of dementia.

In conclusion, the prevalence of all-cause dementia and AD has increased significantly over the past 20 years in a general population of Japanese elderly. The increasing trend seemed to be observed among subjects aged 75 or older. It is important to establish effective prevention strategies for dementia, particularly for AD, in countries such as Japan, where the elderly population is increasing rapidly.

Declaration of interest

None.

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NEURO

Deterioration of abstract reasoning ability in mild cognitive impairment and Alzheimer's disease: correlation with regional grey matter volume loss revealed by diffeomorphic anatomical registration through exponentiated lie algebra analysis

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Abstract
Objective To determine which brain regions are relevant to deterioration in abstract reasoning as measured by Raven's Colored Progressive Matrices (CPM) in the context of dementia.
Methods MR images of 37 consecutive patients including 19 with Alzheimer's disease (AD) and 18 with amnestic mild cognitive impairment (aMCI) were retrospectively analyzed. All patients were administered the CPM. Regional grey matter (GM) volume was evaluated according to the regimens of voxel-based morphometry, during which a non-linear registration algorithm called Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra was employed. Multiple regression analyses were used to map the regions where GM volumes were correlated with CPM scores.
Results The strongest correlation with CPM scores was seen in the left middle frontal gyrus while a region with the largest volume was identified in the left superior temporal gyrus. Significant correlations were seen in 14 additional regions in the bilateral cerebral hemispheres and right cerebellum.
Conclusion Deterioration of abstract reasoning ability in AD and aMCI measured by CPM is related to GM loss in multiple regions, which is in close agreement with the results of previous activation studies.

Keywords Magnetic resonance imaging · Brain · Dementia · Alzheimer's disease · Mild cognitive impairment

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Introduction

Raven's colored progressive matrices (CPM) is a set of psychological tests for abstract reasoning developed by JC Raven in 1947 [1]. It is a less demanding form of the Raven's Standard Progressive Matrices (RSPM) [2] designed especially for children and the elderly with learning handicaps. The examinee is asked to choose the missing segment of the test item to complete a large pattern. CPM consists of three sets, each containing 12 items. Two of the 3 sets (sets A and B) are from RSPM, and an additional 12 items are inserted between sets A and B as set Ab. The test is of widespread international use because of its ease of use and non-verbal nature. For the same reasons, CPM is sometimes incorporated into the screening test for dementia.

Despite its popularity, there are no published data regarding which brain regions are related to deteriorations in performance on this test in the context of dementia. The purpose of this study was to address this question. Many

previous studies have shown that Alzheimer's disease (AD) is associated with a loss of regional grey matter (GM) volume [3–6], likely reflecting histopathological degeneration [7, 8]. Amnestic mild cognitive impairment (aMCI) is considered to be prodromal stage of AD [9]. We studied the correlation between the deterioration of abstract reasoning ability as measured by CPM in AD and aMCI and loss of regional GM volume on high-resolution magnetic resonance (MR) images by means of voxel-based morphometry (VBM) [10].

Materials and methods

Subjects

This study was approved by the regional institutional review board. Informed consent was waived for the retrospective use of MR images and clinical data of patients with AD or aMCI.

We retrospectively analyzed MR data for a total of 37 consecutive patients, including 19 AD patients (6 male;13 female, age range 54 to 84, mean ± SD=74.3±7.2) and 18 aMCI patients (3 male and 15 female, age range 65 to 86, mean ± SD=75.4±5.9). All AD cases were carefully diagnosed in case conferences by both experienced neurologists and psychiatrists at our hospital, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke in concert with the Alzheimer's Disease and Related Disorders Association [11], and the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [12]. Brain MR imaging and perfusion SPECT were routinely performed for the diagnosis of AD. Thus the results of structural MR imaging and SPECT were used as adjuncts. The presence of brain atrophy on structural MR images, especially in the regions of the hippocampus, the medial temporal lobe and the parietal lobe supported the diagnosis of AD. MRI was also used to carefully exclude vascular dementia, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neuroscience [13]. Also, the selective decrease in perfusion in the posterior cingulate gyrus, temporal lobe and parietal lobe on SPECT supported the diagnosis of AD. A diagnosis of aMCI was made based on the Petersen criteria, with memory complaint but otherwise normal cognition and normal daily living activities [9]. These individuals had a clinical dementia rating score [14] of 0.5 or lower.

All patients received both Japanese versions of CPM and the Mini-Mental State Examination (MMSE) [15]. In addition to the raw scores of CPM, we calculated the normalized CPM score (%CPM) by dividing the raw CPM score by average CPM achievement in each decade of life, as previously reported by Sugishita and Yamasaki [16], based on their observations of 299 healthy Japanese individuals.

MR imaging

Images were obtained using a 3.0 T MR imager and an 8-channel head array receiving coil. High-resolution T1-weighted turbo field echo MR images were obtained at the following parameters: TR = 8.1 ms, TE = 3.7 ms, TI = 240 ms, flip angle = 8°, SENSE factor = 2, NSA = 1, FOV = 240 mm, matrix size = 240×240, slice thickness = 1 mm, imaging time = 5 min 20 s. The images were obtained in sagittal planes and were reconstructed into 1-mm-thick contiguous transverse images.

Spatial preprocessing of the MR images

Images were analyzed according to the regimens of VBM on Statistical Parametric Mapping 8 (SPM8) software (Welcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The images were first segmented into the GM and white matter (WM) images. Then, using the segmentation results, roughly aligned GM images were obtained so that the images could be imported for subsequent non-linear registration based on an algorithm called Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) [17]. The voxel size of the imported GM images was $1.5\times1.5\times1.5$ mm^3. The GM images of all subjects were non-linearly registered to the "template", which was created by averaging all individual GM images. Eighteen cycles were repeated to create a more precise template image while updating the average template image after every 3 iterations. The GM images of each subject were registered to the final template while preserving the amount of GM in each voxel by applying "modulation", and spatially normalized into a common stereotaxic space (Montreal Neurological Institute space or MNI space). The images were then smoothed using a Gaussian kernel with a full width of half maximum of 8 mm. Figure 1 shows the original T1-weighted image, the corresponding image of GM segment and the "modulated", normalized and smoothed GM image of an AD patient for illustration purpose.

Statistical analyses

Correlation between the CPM and MMSE scores as well as that between %CPM and MMSE were evaluated using Pearson's correlation coefficients.

A multiple regression analysis was used on SPM8 to map the brain regions where the GM volumes were significantly correlated with total CPM scores while controlling the effects of age and sex of the patients as

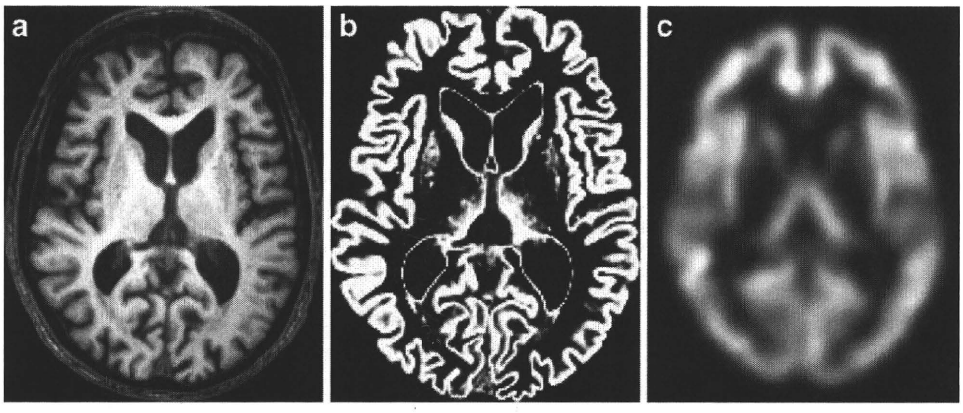

Fig. 1 The original T1-weighted image (**a**), the corresponding image of GM segment (**b**) and the "modulated", spatially normalized and smoothed GM image (**c**) of a 76-year old male patient with Alzheimer's disease

well as clinical diagnosis (aMCI vs AD). Mapping for correlation between local GM volumes and %CPM was performed in the same manner. In addition, mapping for the correlation between local GM volumes and total MMSE scores was also performed. In all mappings, the voxel-level significance threshold was set at $p<0.001$ (uncorrected for multiple comparisons). The extent threshold was set at 50 voxels.

Results

Examination scores

The total CPM scores for all patients ranged from 8 to 35 (mean ± SD=25.2±5.9) out of 36 points. Their ranges for AD and aMCI were 8 to 35 (mean ± SD=22.3±6.5) and 24 to 34 (mean ± SD=28.2±2.8), respectively. The %CPM for all patients ranged from 30 to 126 (mean ± SD=92.9±20.4), with AD and aMCI ranges of 30 to 108 (mean ± SD=81.6±21.1) and 86 to 126 (mean ± SD=104.8±10.7), respectively. The MMSE scores of the 37 patients ranged from 15 to 29 (mean ± SD=24.1±4.0) out of 30 points. Their ranges for AD and aMCI were 15 to 29 (mean ± SD=21.6±3.9) and 23 to 29 (mean ± SD=26.8±1.7), respectively. A significant correlation was found between the raw CPM scores and MMSE scores ($r=0.71$, $p<0.0001$). The correlation between %CPM and MMSE was slightly higher ($r=0.73$, $p<0.0001$) than that between the raw CPM and MMSE scores.

VBM correlation analysis between local GM volume and examination scores

Figure 2 shows the rendered maps of brain regions where local GM volumes were significantly positively correlated with raw CPM scores and also shows regions with a significant positive correlation with MMSE scores. The location, Brodmann area, size (voxels) and peak Z value of the detected brain regions are tabulated in Table 1 for CPM and in Table 2 for MMSE. The strongest correlation with CPM scores was seen in the left middle frontal gyrus while a region with the largest volume was identified in the left superior temporal gyrus. Correlations were seen in 14 other regions including bilateral frontal and temporal lobes, the left parietal lobe, the right occipital lobe, the right putamen, and the right cerebellum. At the same statistical threshold, correlation mapping for MMSE resulted in the detection of fewer regions in comparison with the mapping of CPM. There were only three brain regions in the bilateral parietal lobes (Table 2, Fig. 2). Brain regions where the local GM volume showed a significant positive correlation with %CPM had a similar topographical pattern to that of correlation mapping for raw CPM scores (Table 3).

Discussion

While we are not aware of any previous imaging studies regarding functional activations during performance of CPM, several researchers have reported activations during RSPM tasks. One of the earliest was a functional MRI study by Probhakaran et al. [18], in which they found activations in bilateral frontal lobes (middle and inferior frontal gyri, premotor areas and rostral prefrontal region), bilateral parietal lobes (superior and inferior parietal lobules, supramarginal and angular gyri), occipital lobes (precuneus, lingual gyri, medial and superior occipital gyri) and temporal lobes (middle and inferior temporal gyri). Recently, Perfetti et al. [19] studied brain activation by RSPM using functional MR imaging to elucidate brain regions related to fluid intelligence. They found activations in the pre-supplementary motor area, premotor area, dorsolateral prefrontal cortex, anterior insula, posterior part of inferior temporal gyrus, precuneus, and intraparietal sulcus. More recently, another functional MR imaging study of RSPM was published by Soulieres et al. [20]. They used RSPM to assess altered visual processing in autism. Their healthy control subjects showed activations related to RSPM in premotor areas, the primary motor

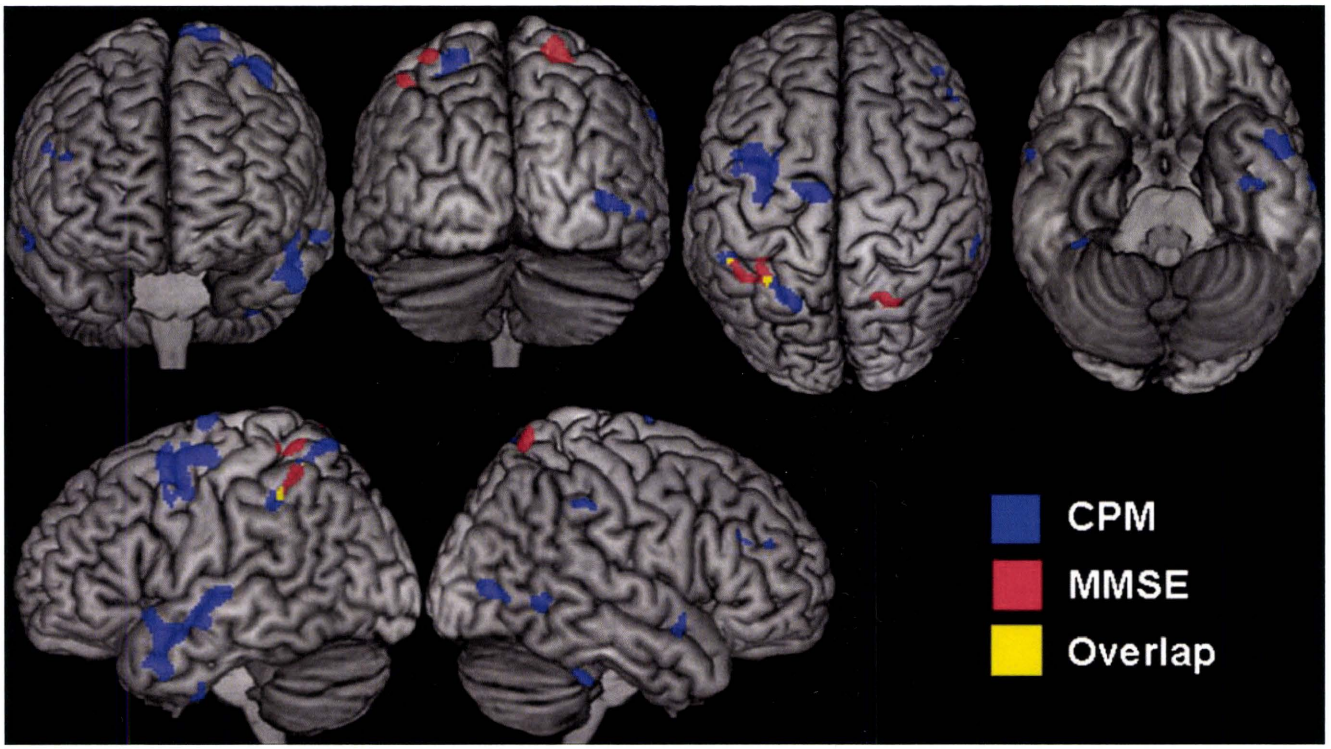

Fig. 2 Rendered maps of regions where the regional grey matter volume was significantly positively correlated with CPM (*blue areas*) and with MMSE (*red areas*) scores, respectively. Their overlaps are indicated as yellowish areas

cortex, inferior frontal gyrus, insula, superior and inferior parietal lobules, precuneus and bilateral occipital lobes. In these previous results, the most consistent findings seem to be activations in the bilateral frontal and parietal lobes. Such concomitant activations in the frontal and parietal lobes have previously been found during performance of visual working memory tasks [21]. Jung and Haier [22] hypothesized that the neural basis of human intelligence is attributable to activities in the frontal-parietal functional network. In their hypothesis, collected visual and auditory information is processed in the occipital and temporal cortices, and then fed forward to the parietal cortex, where

Table 1 Regions where regional gray matter volume was significantly positively correlated with CPM scores

Location	BA	MNI coordinate (mm)			Z score	Extent (voxels)
		x	y	z		
Left middle frontal gyrus	6	−39	0	63	4.74	1,093
Left superior temporal gyrus	22	−51	−9	−8	4.44	1,892
Left inferior frontal gyrus	6	−36	9	34	4.16	337
Right middle occipital gyrus	19	42	−76	3	4.08	217
Left superior frontal gyrus	6	−9	−12	79	3.83	347
Left inferior parietal lobule	40	−69	−45	34	3.80	153
Right middle frontal gyrus	46	54	35	25	3.75	170
Right cerebellum anterior lobe	NA	41	−38	−35	3.73	58
Right middle temporal gyrus	21	45	−49	−2	3.66	216
Left inferior parietal lobule	40	−53	−40	43	3.55	87
Left superior parietal lobule	7	−24	−60	64	3.54	233
Right middle temporal gyrus	21	65	5	−36	3.51	51
Right inferior parietal lobule	40	68	−34	43	3.49	139
Right middle temporal gyrus	21	65	5	−15	3.45	136
Left inferior temporal gyrus	20	−44	−7	−38	3.37	122
Right putamen	NA	32	0	−5	3.28	73

BA Brodmann area; *MNI* Montreal Neurological Institute; *NA* not applicable

Table 2 Regions where regional gray matter volume was significantly positively correlated with MMSE scores

Location	BA	MNI coordinate (mm)			Z score	Extent (voxels)
		x	y	z		
Left superior parietal lobule	7	−38	−49	69	3.88	228
Left inferior parietal lobule	40	−44	−51	55	3.80	97
Right superior parietal lobule	7	18	−60	71	3.44	163

BA Brodmann area; *MNI* Montreal Neurological Institute

structural symbolism, abstraction and elaboration emerge. Through the WM network, the parietal cortex interacts with the frontal cortex which serves to test various solutions to a given problem. As explained in their hypothesis, activations in the occipital and temporal lobes during the RSPM, which have been reported in some of the previous studies, seem to reflect a higher order processing of visual input [23].

The brain regions whose GM volumes were found to be correlated with the CPM scores in our study in most parts overlap the results of the activation studies described above. Specifically, significant correlations of the CPM deterioration with GM volume loss in the bilateral middle and left inferior frontal gyri, bilateral inferior parietal and left superior parietal cortices, and right middle and left inferior temporal gyri can be accounted for by the results of those functional MR imaging studies on RSPM [18–20]. In the present study, the largest cluster was found in the left superior temporal gyrus (Tables 1 and 3, Fig. 2). This area has been previously reported to be involved in attentional control in a visual task [24]. Although activation of this area has not been shown in the functional activation by RSPM [18–20], impaired attentional control due to neurodegenerative damage in this brain region might have resulted in a deterioration of CPM task performance.

We found a high correlation between the CPM and MMSE scores (r=0.71 between CPM and MMSE, and r=0.73 between %CPM and MMSE), confirming the usefulness of CPM in assessing the severity of dementia. It should be noted, however, that mean the %CPM score for aMCI patients was over 100 (104.8). CPM seems to be relatively insensitive to early cognitive changes in dementia. The results of VBM analyses for the CPM and MMSE were very different. The local GM volume was significantly correlated with MMSE scores only in the bilateral parietal cortices (Table 2 and Fig. 2). Several previous studies have been published regarding the correlation between MMSE scores and local GM loss in AD and aMCI [25–28]. Our result regarding the correlation between GM volume and MMSE is consistent with a previous report by Apostolova et al. [26] who performed whole brain mapping of GM density in AD and aMCI patients, and found that the bilateral superior parietal cortices were among the brain regions with the strongest correlations with MMSE scores. Compared to the results of CPM obtained at the same statistical threshold, the extent of the GM regions correlated with MMSE was much more limited (Fig. 2). This is likely due to the nature of MMSE: it is designed for the assessment of "general" cognitive status rather than specific

Table 3 Regions where regional gray matter volume was significantly positively correlated with %CPM

Location	BA	MNI coordinate (mm)			Z score	Extent (voxels)
		x	y	z		
Left middle frontal gyrus	6	−39	0	63	4.99	1,254
Left superior temporal gyrus	22	−51	−10	−8	4.40	1,148
Left inferior frontal gyrus	6	−35	8	33	4.33	323
Right cerebellum, anterior lobe	NA	41	−36	−36	3.97	90
Left superior frontal gyrus	6	−11	−10	79	3.93	428
Right middle occipital gyrus	19	42	−76	3	3.84	159
Left inferior parietal lobule	40	−69	−45	34	3.83	190
Left superior parietal lobule	7	−24	−58	63	3.78	314
Left inferior parietal lobule	40	−53	−40	43	3.75	189
Right middle frontal gyrus	46	54	35	25	3.62	91
Right middle temporal gyrus	21	54	−54	0	3.58	171
Left inferior temporal gyrus	20	−36	−7	−48	3.56	304
Right inferior parietal lobule	40	68	−34	43	3.53	188
Right putamen	NA	32	2	−3	3.22	53

BA Brodmann area; *MNI* Montreal Neurological Institute; *NA* not applicable

brain function, and thus it consists of several different types of tasks (arithmetic, memory, and orientation) that may involve the activities of several distinct brain regions. Therefore, a deterioration of MMSE score may not be associated with damage to specific brain regions. The different results obtained in this study from correlation mapping with CPM and MMSE suggest from a radiological perspective that assessment of the patient's cognitive status should be based on a battery of psychiatric tests rather than a single scale.

This study has several limitations. First, some GM regions such as the entorhinal cortex and hippocampus are more affected by AD, and volume loss in those regions may also occur in such early stages as aMCI [4, 29]. Our study involved only patients with aMCI and AD, and normal individuals were not included. Thus among our study subjects, early volume losses in those specific brain regions might have been overlooked, resulting in an underestimation of the correlation between psychological deterioration and local GM volume loss. Inclusion of normal subjects may correct such biases. Second, the results of VBM correlation analysis should be disease-specific, and may not represent the complete picture of brain regions relevant to CPM performance. As such, these results must be interpreted with care.

In conclusion, we used VBM analysis with DARTEL non-linear registration to study correlations between the regional GM volume and CPM scores in AD and aMCI. We found that deterioration in abstract reasoning ability as measured by CPM was correlated with local GM losses in multiple regions of the bilateral cerebral cortices and right cerebellum.

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Insulin resistance is associated with the pathology of Alzheimer disease

The Hisayama Study

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ABSTRACT

Objective: We examined the association between diabetes-related factors and pathology of Alzheimer disease (AD) to evaluate how diabetes affects the pathogenic process of AD.

Methods: This study included specimens from a series of 135 autopsies of residents of the town of Hisayama in Fukuoka prefecture (74 men and 61 women) performed between 1998 and 2003, who underwent a 75-g oral glucose tolerance test in clinical examinations in 1988. We measured diabetes-related factors including fasting glucose, 2-hour post-load plasma glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) in 1988. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines and neurofibrillary tangles (NFTs) were assessed according to Braak stage. The associations between each factor and AD pathology were examined by analysis of covariance and logistic regression analyses.

Results: Higher levels of 2-hour post-load plasma glucose, fasting insulin, and HOMA-IR were associated with increased risk for NPs after adjustment for age, sex, systolic blood pressure, total cholesterol, body mass index, habitual smoking, regular exercise, and cerebrovascular disease. However, there were no relationships between diabetes-related factors and NFTs. Regarding the effects of *APOE* genotype on the risk of AD pathology, the coexistence of hyperglycemia and *APOE* ϵ4 increased the risk for NP formation. A similar enhancement was observed for hyperinsulinemia and high HOMA-IR.

Conclusion: The results of this study suggest that hyperinsulinemia and hyperglycemia caused by insulin resistance accelerate NP formation in combination with the effects of *APOE* ϵ4.

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GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **FPG** = fasting plasma glucose; **GSK3** = glycogen synthase kinase 3; **HOMA-IR** = homeostasis model assessment of insulin resistance; **IDE** = insulin-degrading enzyme; **NFT** = neurofibrillary tangle; **NP** = neuritic plaque; **OGTT** = oral glucose tolerance test; **OR** = odds ratio; **PG** = post-load plasma glucose.

The prevalence of diabetes is growing at epidemic proportions worldwide, and is becoming a major health problem. Several large longitudinal population-based studies have shown that the rate of cognitive decline is accelerated in elderly people with type 2 diabetes compared with the general population.[1-3] Similarly, other epidemiologic studies have revealed that diabetes increases the risk of dementia,[2,4-7] including Alzheimer disease (AD), which is the most common cause of dementia in late life.[2,4,5,8,9] Therefore, the effect of diabetes on cognitive function in the elderly has significant public health implications.

Several lines of evidence indicate a role of insulin and glucose metabolism on the risk of developing dementia, including AD.[10-14] Many mechanisms through which diabetes could increase the risk of dementia have been postulated, and include glucose toxicity, insulin resis-

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tance, oxidative stress, advanced glycation end products, inflammatory cytokines, and microvascular and macrovascular disease.[15] However, the determinant pathway, which is more critical to AD pathogenesis, is less clear. Understanding the role of disease-related risk factors for AD pathogenesis may help to identify specific modifiable risk factors that could enable the prevention of AD.[16] Therefore, identifying the dominant pathway through which diabetes influences the pathogenic process of AD may have benefits for public health.

To clarify the relationship between diabetes and AD, we searched for evidence of AD-related pathologic risk by examining the associations between diabetes-related factors and typical AD-related pathologic outcomes, neuritic plaques (NPs) and neurofibrillary tangles (NFTs).

METHODS

Subjects. Since 1961, we have been conducting a long-term prospective cohort study of cerebro-cardiovascular diseases in the town of Hisayama, a suburb of the city of Fukuoka in southern Japan. The design of the Hisayama Study has been described in detail elsewhere.[17-19] In the present study, we examined a series of autopsy samples of Hisayama residents from October 1, 1998, to March 31, 2003. During this period, 290 residents in Hisayama died and 214 were autopsied (autopsy rate: 73.8%). The clinical data for the present study were collected from a clinical examination performed in 1988, as described previously.[19] Briefly, of a total of 3,390 residents aged over 40 years included in this registry, 2,742 (participation rate, 80.9%) took part in a clinical examination in 1988. Of these, a 75-g oral glucose tolerance test (OGTT) was performed in 2,520 subjects. Of the 214 autopsy cases, we excluded 3 subjects whose brain specimens were inadequate for evaluation, and 76 subjects who did not complete the OGTT in 1988. Finally, 135 subjects who underwent both the OGTT and brain autopsy were included in the present study. None of the 135 subjects showed signs of dementia at the clinical examination in 1988. Careful surveillance of cognitive impairment was carried out through a daily monitoring system established by the study team, local practitioners, and the town government.[9,18]

Standard protocol approvals, registrations, and patient consents. The study was approved by the Ethics Committee of the Faculty of Medicine, Kyushu University, and was performed in accordance with the ethical standards described in the 5th revision of the Declaration of Helsinki, 2000. Written informed consent was obtained from all study subjects.

Risk factors. In the clinical examination performed in 1988, the 75-g OGTT was performed after at least a 12-hour overnight fast and the following 3 diabetes-related factors were determined: fasting plasma glucose (FPG), 2-hour post-load plasma glucose (2-hour PG), and fasting insulin. Glucose was determined by the glucose oxidase method and fasting insulin was determined by a radioimmunoassay. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: FPG (mmol/L) × fasting insulin (μU/mL)/22.48155.[20] Blood pressure was measured 3 times at the right upper arm using a mercury sphygmomanometer after at least 5 minutes of rest in a sitting position; the mean of the 3 measurements was used in the analysis. Total cholesterol levels were determined enzymatically. Height and weight were measured in light clothes without shoes, and body mass index (BMI; weight/height squared, kg/m^2) was calculated. Information on exercise and smoking habits was obtained via a standard questionnaire, and these factors were classified as being habitual or not. Regular exercise means engaging in sports or other forms of exertion regularly more than 3 times per week during leisure time. *APOE* genotyping was determined by direct sequencing at Takara Bio Inc., Japan. No homozygous ϵ4 genotype was found among these participants, and those who carried 1 copy of the ϵ4 allele were categorized as *APOE* ϵ4 carriers.

Assessment of neuropathologic changes. The assessment of AD pathology was conducted according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) guidelines and Braak stage established by Braak and Braak.[21-23] Brains were fixed in 10% buffered formalin for at least 2 weeks. Brain specimens in each case included the middle frontal gyrus, superior and middle temporal gyri, inferior parietal lobule, anterior cingulated gyrus, amygdala, hippocampus with entorhinal and transentorhinal cortex (at the level of the lateral geniculate body), calcarine cortex, basal ganglia including the nucleus basalis of Meynert, thalamus, substantia nigra, locus ceruleus, and dorsal vagal nucleus. Sections were embedded in paraffin and were routinely stained using hematoxylin-eosin, Klüver-Barrera, and a modified Bielschowsky method. Specimens from each subject were immunostained with antibodies against phosphorylated tau (AT8, mouse monoclonal, 1:500; Innogenetics, Belgium). Immunolabeling was detected using a standard indirect immunoperoxidase method and visualized using diaminobenzidine (Dojindo, Japan) as a chromogen. The frequency of NPs defined by the CERAD criteria were semiquantitatively categorized into the following 4 groups: none (score 0), sparse (score 1), moderate (score 2), and frequent (score 3). The extent of NFTs according to Braak stage was semiquantitatively classified into the following 4 groups: stage 0, stage I to II, stage III to IV, and stage V to VI. For the pathologic assessment of cerebrovascular diseases, any types of cerebral infarctions and hemorrhages were registered according to gross examination and microscopic assessment, regardless of clinical features. This factor was classified as being present or not.

Statistical analyses. Statistical analyses were conducted using SAS software version 9 (SAS Institute, Cary, NC). Mean or geometric mean values of the diabetes-related factors among the groups of NPs or NFTs were calculated and compared by analysis of covariance, with adjustment for age at clinical examination and sex. We used logistic regression analysis to determine relationships between the risk factors (diabetes-related factors, *APOE* genotype, and their interaction) and pathologic outcome (presence or absence of NPs and NFTs) and are expressed as odds ratios (OR) and 95% confidence intervals (CI). Continuous variables (FPG, fasting insulin, and HOMA-IR) were divided into 3 groups to compare the risk of NPs among tertiles. Missing values (1 for fasting insulin, 1 for HOMA-IR, 6 for *APOE* ϵ4 carrier, and 1 for the grading of Braak stage) were excluded from the analysis. Age at clinical examination was used for adjustment in the present study; adjustment for age at death resulted in equivalent statistical outcomes. Significance was de-

Table 1 **Demographic characteristics of the study subjects (n = 135)[a]**

Variables	Values
Male sex	54.8
Age at medical examination, y	67.0 ± 9.5
Fasting plasma glucose, mmol/L	5.9 ± 1.2
2-hour post-load plasma glucose, mmol/L	8.3 ± 4.3
Fasting insulin, μU/mL[b,c]	5.2 (2.0-13.6)
HOMA-IR[b,c]	1.3 (0.5-4.0)
Systolic blood pressure, mm Hg	138.7 ± 23.6
Diastolic blood pressure, mm Hg	76.5 ± 12.1
Serum total cholesterol, mmol/L	5.2 ± 1.1
BMI, kg/m^2	22.0 ± 3.2
Current smoking	32.6
Regular exercise[d]	11.1
APOE ε4 carrier[c]	19.4

Abbreviations: BMI = body mass index; HOMA-IR = homeostasis model assessment of insulin resistance.
[a] Values are means ± SD or percentage.
[b] Geometric means and 95% prediction intervals are shown for fasting insulin and HOMA-IR due to their skewed distributions.
[c] Missing values: 1 for fasting insulin, 1 for HOMA-IR, and 6 for *APOE* ε4 carrier.
[d] Engaging in sports or other forms of exertion regularly more than 3 times per week during leisure time.

fined as $p < 0.05$, and marginal significance was defined as $0.05 \leq p < 0.10$ in statistical analysis.

RESULTS The characteristics of the study subjects at clinical examination in 1988 (n = 135) are described in table 1. Mean ± SD age at clinical examination was 67.0 ± 9.5 and mean ± SD age at death was 79.5 ± 9.3 years, and 54.8% (n = 74) of the subjects were male. Overall, 19.4% (n = 25) of subjects were carrying *APOE* ε4. There was no selection bias regardless of autopsy, according to a comparison of demographic characteristics between our study subjects and those who did not undergo autopsy (data not shown). Out of the 135 subjects, 15.6% (n = 21) developed Alzheimer-type dementia. Based on the assessment of AD pathology, the frequencies of NPs were categorized into the following 4 groups by CERAD criteria: 34.8% (n = 47) for none (score 0), 17.0% (n = 23) for sparse (score 1), 14.1% (n = 19) for moderate (score 2), and 34.1% (n = 46) for frequent (score 3). The frequencies of NFTs were classified into the following 4 groups by Braak stage: 14.2% (n = 19) for stage 0, 18.7% (n = 25) for stage I to II, 44.0% (n = 59) for stage III to IV, and 23.1% (n = 31) for stage V to VI. Prevalence of cerebrovascular disease at autopsy was 59.3% (n = 80), which included any types of infarctions (n = 73) and hemorrhages (n = 10).

As shown in table 2, we compared the age- and sex-adjusted mean (or geometric mean) values of diabetes-related factors among groups according to CERAD score for NPs or Braak stage for NFTs. The subjects with NPs (CERAD score 1 to 3) showed significantly higher levels of 2-hour PG, fasting insulin, and HOMA-IR than those without NPs (CERAD score 0). However, there was no obvious dose-response relationship between these variables and CERAD score. The FPG levels remained broadly constant irrespective of CERAD score. Regarding the frequencies of NFTs, we found no relationship between any diabetes-related factor and Braak stage.

As shown in table 3, we estimated the effect of each diabetes-related factor on the presence of AD pathology using logistic regression analysis. As for NPs, elevated 2-hour PG significantly increased the risk of NPs in the age- and sex-adjusted analysis (model 1). Similarly, hyperinsulinemia and high HOMA-IR were also significant positive risk factors

Table 2 **Age- and sex-adjusted means of glucose, insulin, and HOMA-IR according to CERAD score and Braak stage[a]**

	Frequency of NPs (CERAD score)				p Value (CERAD score 1-3 vs 0)	Frequency of NFTs (Braak stage)				p Value (Braak stage I-IV vs 0)
	0	1	2	3		0	I, II	III, IV	V, VI	
Fasting plasma glucose, mmol/L	5.7	6.0	6.2	5.9	0.22	5.7	6.1	5.8	6.0	0.38
2-hour post-load plasma glucose, mmol/L	7.2	9.0[c]	9.6[b]	8.7	0.03	7.0	9.2[c]	8.4	8.5	0.13
Fasting insulin, μU/mL	4.6	6.1[b]	5.2	5.6[c]	0.03	5.1	5.0	5.2	5.7	0.81
HOMA-IR	1.2	1.6[b]	1.4	1.4[c]	0.02	1.3	1.4	1.3	1.5	0.62

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; HOMA-IR = homeostasis model assessment of insulin resistance; NP = neuritic plaque.
[a] Geometric means for fasting insulin and HOMA-IR are shown due to their skewed distributions.
[b] $p < 0.05$, [c] $p < 0.10$ vs CERAD score = 0 or Braak stage = 0.

Table 3 **Odds ratios and 95% confidence intervals for the presence vs absence of neuritic plaques and neurofibrillary tangles[a]**

	OR for presence of NPs (CERAD score 1-3 vs 0)				OR for presence of NFTs (Braak stage I-VI vs 0)			
	Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Fasting plasma glucose, mmol/L	1.33 (0.86-2.04)	0.20	1.41 (0.88-2.26)	0.15	1.31 (0.72-2.37)	0.38	1.35 (0.74-2.47)	0.33
2-hour post-load plasma glucose, mmol/L	1.66 (1.04-2.63)	0.03	1.71 (1.04-2.80)	0.03	1.58 (0.85-2.93)	0.15	1.67 (0.88-3.17)	0.12
Fasting insulin, μU/mL	1.61 (1.04-2.48)	0.03	2.03 (1.11-3.70)	0.02	1.05 (0.62-1.79)	0.85	1.06 (0.55-2.04)	0.86
HOMA-IR	1.67 (1.08-2.59)	0.02	2.11 (1.18-3.79)	0.01	1.14 (0.66-1.98)	0.64	1.19 (0.62-2.30)	0.60

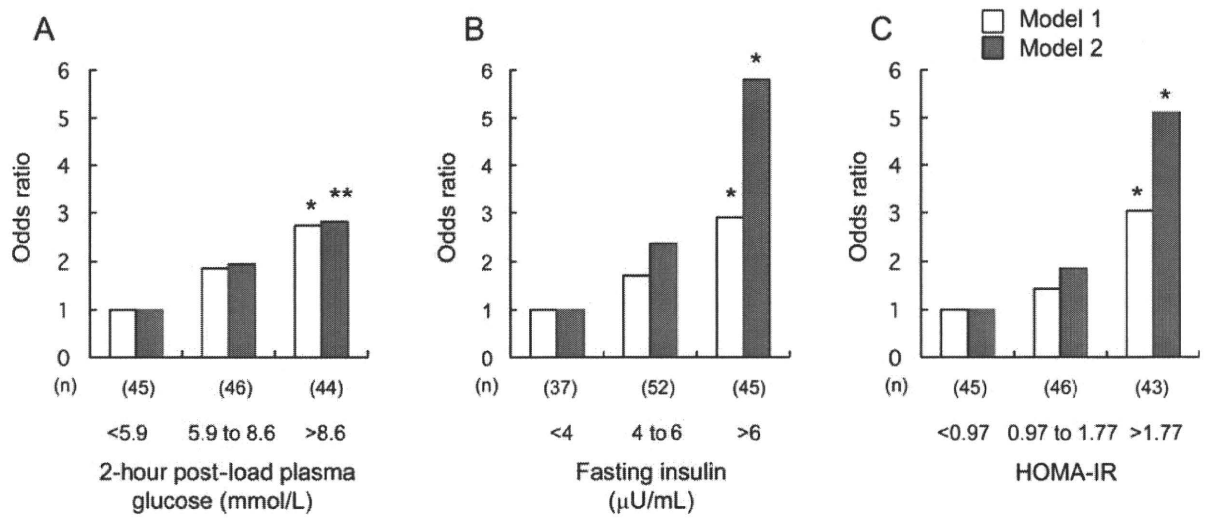
Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; HOMA-IR = homeostasis model assessment of insulin resistance; NP = neuritic plaque; NFT = neurofibrillary tangle; OR = odds ratio.
[a] Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, total cholesterol, body mass index, current smoking, regular exercise, and cerebrovascular disease. ORs are given for each 1-SD increase in glucose, or log fasting insulin and HOMA-IR values.

for NPs. However, there was no relationship between FPG and NPs. These results were almost the same in the multivariate analyses after adjustment for age, sex, systolic blood pressure, total cholesterol, BMI, current smoking, regular exercise, and cerebrovascular disease (model 2). We repeated analyses after excluding the 21 cases with cognitive impairment, and the associations remained unchanged. On the other hand, we found no significant association between diabetes-related factors and NFT pathology (Braak stage I to VI vs stage 0).

To confirm the association between diabetes-related factors and NPs, we compared the risk of NPs among tertiles of 2-hour PG, fasting insulin, and HOMA-IR (figure 1). Compared with the lowest tertile of 2-hour PG (<5.9 mmol/L), the risk of NPs was significantly increased in the highest tertile (>8.6 mmol/L) after adjustment for age and sex (model 1). After adjustment for the aforementioned confounding factors (model 2), this relationship was marginally significant. On the other hand, the highest tertiles of fasting insulin (>6 μU/mL) and HOMA-IR (>1.77) showed increased risk for NPs compared with the lowest tertiles (<4 μU/mL for insulin, <0.97 for HOMA-IR) in models 1 and 2.

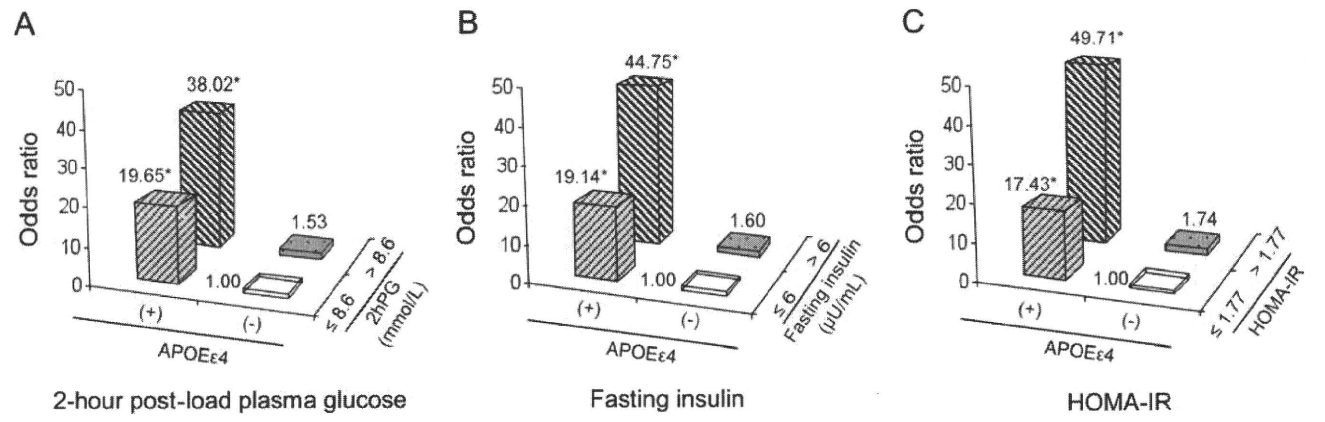
Finally, we examined the combined effects of *APOE* genotype and the magnitude of the diabetes-related factors on the risk of NP pathology (figure 2). For example, the subjects were classified into the following 4 groups according to the 2-hour PG level

Figure 1 **Odds ratios for each tertile of glucose (A), insulin (B), and HOMA-IR (C) vs the lowest tertile for the presence of neuritic plaques**



Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, systolic blood pressure, total cholesterol, body mass index, current smoking, regular exercise, and cerebrovascular disease. *$p < 0.05$, **$p < 0.10$ vs the lowest tertile. HOMA-IR = homeostasis model assessment of insulin resistance.

Figure 2 **Odds ratios for the presence of neuritic plaques according to diabetes-related risk factors and *APOE* genotype**



Adjusted for age, sex, and total cholesterol. The numbers in the figure are odds ratios vs the reference group (*APOE* ε4 noncarrier and lower level of glucose [A], insulin [B], or HOMA-IR [C]). *$p < 0.05$ vs reference group. 2hPG = 2-hour post-load plasma glucose; HOMA-IR = homeostasis model assessment of insulin resistance.

and *APOE* status: low 2-hour PG (lowest and second tertiles, ≤8.6 mmol/L) and noncarriers of *APOE* ε4 (group 1), high 2-hour PG (highest tertile, >8.6 mmol/L) and noncarriers of *APOE* ε4 (group 2), low 2-hour PG and *APOE* ε4 carriers (group 3), and high 2-hPG and *APOE* ε4 carriers (group 4). The ORs for the presence of NPs in these 4 groups were 1.0 in group 1 (reference), 1.5 in group 2, 19.7 in group 3, and 38.0 in group 4. As a result, the coexistence of hyperglycemia and *APOE* ε4 genotype (group 4) was associated with the greatest risk for NPs. We performed similar analyses with fasting insulin and HOMA-IR, and similar patterns were observed.

DISCUSSION We suggest that hyperglycemia, hyperinsulinemia, and insulin resistance are risk factors for NP pathology in AD, and might affect the initiation of NP formation. The lack of a dose-response relationship, and the absence of a significant association between the diabetes-related factors and NFT pathology, might be due to an epidemiologic competing effect, indicating that subjects with very high diabetes-related factors at the clinical examination in 1988 probably died earlier as a result of cardiovascular disease, for example. Nevertheless, NFT pathology was less associated with diabetes-related factors, and NFT pathology is considered to be a consequence of β-amyloid deposition in the amyloid cascade hypothesis.[24] The diabetes-related factors may act upstream of the cascade, and might trigger the AD pathogenesis.

Type 2 diabetes is based on insulin resistance and involves chronic compensatory hyperinsulinemia and hyperglycemia. Insulin itself may affect amyloid metabolism, which leads to NP formation. An impaired insulin signaling may exacerbate β-amyloid accumulation by a weakened inhibition on glycogen synthase kinase 3 (GSK3), which is thought to be critically involved in AD pathogenesis.[25] Activated GSK3 triggers γ-secretase activity[26] and increases β-amyloid production.[27] Alternatively, excessive β-amyloid can be cleared by endocytosis or through direct extracellular proteolytic degradation by insulin-degrading enzyme (IDE).[28] Insulin seems to inhibit the extracellular degradation of β-amyloid by competition for IDE.[29] Furthermore, several lines of evidence suggest that the toxic effects of hyperglycemia can lead to slowly progressive functional and structural abnormalities in the brain.[30] It is possible that vascular factors induced by metabolic disturbance may modify the AD-related pathology, however, the positive association between diabetes-related factors and NP pathology still remained even after the adjustment for cerebrovascular lesions in our study.

On the contrary, insulin is known to facilitate memory in normal physiology, as demonstrated when administered at optimal doses and in the context of sufficient glucose availability.[31] The formation of NPs, as described above, is a hallmark of AD, which refers to the pathologic entity; meanwhile, Alzheimer dementia, which refers to clinical dementia, may also be caused in part by deficiencies in intracellular and intercellular signaling.[32] Insulin resistance affects insulin signaling, which might lead to a decline in cognitive function. In this study, the subjects who developed Alzheimer dementia were far less than those who manifested NPs (n = 21 vs 88); therefore, the present pathology-based study should overlap, but is also distinct from the previously reported clinicoepidemiologic studies.[2,4,5,8,9] Our target in this study was to evaluate how diabetes affects the neuropathologic process of AD, which would precede the cognitive decline.

Four previous studies have examined the association between diabetes and AD-related pathology, but their results are inconsistent.[5,33-35] Of these, the Honolulu-

Asia Aging Study was the only population-based study and reported that participants with type 2 diabetes and the *APOE* ε4 allele had a higher number of hippocampal NPs and NFTs in the cortex and hippocampus than those without diabetes and the ε4 allele.[5] In our study, the combination of the unfavorable status afforded by the diabetes-related factors and the presence of the ε4 allele was associated with NP formation, but not with NFT formation (data not shown). The discrepancy in these studies may reflect differences in design of these studies. One possibility is the difference in the observation period between the evaluation of diabetes and the autopsy. Because the observation period in our study was relatively long (10–15 years) compared with the Honolulu-Asia Aging Study (<8 years), our study design might reduce the possibility of reverse causality that the presence of AD might affect lifestyle of the subjects and the severity of glucose intolerance. Another possibility is the difference in the study subjects. Both studies were population-based and included Asian subjects; however, the mean age at clinical examination of the Honolulu-Asia Aging Study (78 years) was greater than that in our study. The other 3 studies[33-35] reported controversial or statistically insignificant results between diabetes status and AD pathology, probably due to the facility-based design and different races.

Our study suggests that the combination of each diabetes-related factor and the *APOE* ε4 genotype may have a synergistic effect on the risk of NPs, even though we failed to show a statistically positive interaction (p for interaction = 0.90 [2-hour PG], 0.84 [fasting insulin], 0.79 [HOMA-IR]). The Honolulu-Asia Aging Study[5] also showed synergistic effects of diabetes and the *APOE* ε4 genotype on AD pathology; however, that study did not account for some diabetes-related factors such as insulin levels and HOMA-IR. It was found that apolipoprotein E2 and E3, but not E4, may be involved in β-amyloid clearance.[36] Additionally, apolipoprotein E is commonly colocalized with β-amyloid in NPs,[37] which led to the hypothesis that apolipoprotein E may be involved in β-amyloid aggregation and plaque formation. Because the apolipoprotein E4 isoform stimulates the nucleation and aggregation of β-amyloid in an isoform-specific manner and does not significantly affect the accumulation of β-amyloid deposits,[38] both apolipoprotein E4 and diabetes-related factors may act synergistically on the initiation of β-amyloid aggregation. We consider that a future study using a larger sample size is needed to investigate the interaction between each diabetes-related factor and the *APOE* genotype on the risk of AD pathology.

There are some limitations to our present study. First, the crude, semiquantitative evaluation of NPs (CERAD) and NFTs (Braak stage) could affect the statistical analyses. Second, the medical history of diabetes, such as disease duration, glucose control, and complications, were not considered in this study. Despite these limitations, our study has several strengths. We included community-based subjects, who had detailed metabolic characterization at midlife based on comprehensive blood testing, which included 75-g OGTT profiles and fasting insulin levels, and we systematically assessed AD pathology. Accordingly, the data included in this study are of value to examine the metabolic risk factors for AD pathology. In the Hisayama Study, both participation rate of clinical examinations and autopsy rate have remained at high levels. Therefore, our results could apply to other Japanese populations.

Further studies are required to determine if there is a causal link between insulin resistance and the development of NPs or other AD-related neuropathologies. In the future, adequate control of diabetes might contribute to a strategy for the prevention of AD.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. T. Matsuzaki.

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