Hypertension Research (2010) 33, 916–921

www.nature.com/hr

ORIGINAL ARTICLE

QT interval prolongation and the risks of stroke and coronary heart disease in a general Japanese population: the Hisayama study

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Uncertainty remains regarding the value of heart-rate-corrected QT interval (QTc) prolongation on electrocardiogram for predicting cardiovascular disease (CVD), particularly among Asian populations. The objective of the present analysis was to analyze the association of QTc prolongation with the development of CVD in a general Japanese population. During the follow-up period, 303 CVD events were observed. Among men, the age-adjusted incidence rates of CVD rose with prolonged QTc levels: 10.9, 12.1, 14.1 and 37.8 per 1000 person-years for subgroups defined by QTc levels of <400, 400–419, 420–439 and ⩾440 ms, respectively (*P*=0.0007 for trend). The risk of CVD in the highest group was 3.09-fold (95% confidence interval, 1.82–5.25) higher than that in the lowest group even after controlling for other confounding factors: age, hypertension, heart rate, electrocardiogram abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterols, alcohol intake, smoking habit and regular exercise. Similar associations were observed for the outcomes of stroke and coronary heart disease. Among women, in contrast, no clear associations were found between QTc levels and the risk of CVD events. In conclusion, prolonged QTc levels were associated with the development of CVD among general Japanese men. Measurement of QTc intervals is likely to provide additional information for the detection of individuals at high risk of future CVD events.
Hypertension Research (2010) **33**, 916–921; doi:10.1038/hr.2010.88; published online 10 June 2010

Keywords: coronary artery disease; epidemiology; QT interval; stroke

INTRODUCTION

Heart-rate-corrected QT interval (QTc) prolongation on the resting 12-lead electrocardiogram (ECG) has been associated with an increased risk for ventricular arrhythmia or sudden cardiac death.[1,2] Recently, several epidemiological studies have also shown that QTc prolongation predicts the likelihood of cardiovascular disease (CVD), suggesting a possible link between QTc prolongation and atherosclerosis.[3–7] However, other epidemiological studies found no clear associations between QTc prolongation and the risk of CVD,[7–10] and there is significant uncertainty surrounding the association between QTc prolongation and CVD. Furthermore, current knowledge of the effects of QTc prolongation on CVD was derived mainly from studies conducted in Western populations; it is unclear to what extent these findings apply to Asian populations. The objective of the present analysis was to analyze the longitudinal relationship between QTc prolongation and the future development of stroke and coronary heart disease in a long-term prospective study of a general Japanese population.

METHODS

Study population

Since 1961, we have been conducting a long-term prospective cohort study of CVD in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[11,12] In 1988, a screening survey for this study was performed in the town. Detailed descriptions of this survey have been published previously.[13–16] Briefly, a total of 2736 residents aged 40 years or older (80.7% of the total population of this age group) consented to participate in the examination. Among those, 102 subjects with a history of stroke or coronary heart disease were excluded from the present analysis based on the results of a questionnaire, face-to-face interviews, physical and neurological examinations, 12-lead ECG and, if necessary, other ancillary laboratory examinations. After further exclusion of 165 subjects who had had atrial fibrillation or ventricular conduction defects (QRS interval of 120 ms or longer), 22 subjects with high heart rates (⩾100 beats per minute) and 8 subjects whose ECG recordings were not available, we enrolled the remaining 2439 individuals in this study.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

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Received 23 November 2009; revised 22 March 2010; accepted 16 April 2010; published online 10 June 2010

Follow-up survey

This population was followed up for 14 years, from December 1988 through November 2002, by repeated health examinations or by a daily monitoring system established by the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 479 subjects died, of whom 362 (75.6%) underwent autopsy. Morphologic examinations by autopsy or brain imaging were performed on all stroke patients.[17] Only one subject was lost to follow-up.

Measurements of QTc

Standard, resting 12-lead ECG was recorded on an FCP-270 device (Fukuda Denshi, Tokyo, Japan) in the supine position on the morning of the screening surveys conducted in 1988. Heart rate (beats per minute) and QT interval duration (ms) were determined using ECG analysis software (PI-01, Fukuda Denshi) as described previously.[18] The program calculated the mean values of QT interval duration from the beginning of QRS to the end of the T wave in 12-lead ECG. The average QT interval duration was then corrected for heart rate by calculating QTc according to Bazett's equation (QTc=QT interval duration/(60/heart rate)$^{1/2}$).[19] Groups of participants defined by four QTc ranges (<400, 400–419, 420–439 and ≥440 ms) were used for the analysis.

Risk factors

A self-administered questionnaire covering medical history, alcohol consumption, smoking habit and regular exercise was completed in advance by each participant and was verified by trained interviewers at the baseline screening examination. Alcohol consumption and smoking habit were classified as either habitual or not. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time were assigned to the regular exercise group. Blood pressure was measured three times with the subject in a recumbent position, after having rested for at least 5 min before the first measurement and again for at least 5 min between measurements, by means of a standard sphygmomanometer with a standard cuff.[12,20] Korotkoff phase 5 was taken as the diastolic BP unless the sounds persisted at 0, in which case Korotkoff phase 4 was recorded. The mean of the three measurements was used in the present analysis. Hypertension was defined as blood pressure of ≥140/90 mm Hg or current use of antihypertensive agents. Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥25.0 kg m^{-2}. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code: 3–1) and/or ST depression (Minnesota codes: 4–1, 4–2 or 4–3). To determine serum lipid levels, blood samples were collected from an antecubital vein after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined enzymatically. Dyslipidemia was defined as total cholesterol ≥5.68 mmol l^{-1}, HDL-cholesterol ≤1.03 mmol l^{-1} or triglycerides ≥1.69 mmol l^{-1}. Non-HDL cholesterol was defined as total cholesterol excluding HDL cholesterol. At the baseline examination, we also performed the 75 g glucose tolerance test. Plasma glucose levels were determined by the glucose-oxidase method. Glucose tolerance status was also defined by the 1998 World Health Organization criteria;[21] namely, for impaired fasting glycemia, FPG 6.1–6.9 mmol l^{-1} and 2-h PG <7.8 mmol l^{-1}; for impaired glucose tolerance, FPG <7.0 mmol l^{-1} and 2-h PG 7.8–11.0 mmol l^{-1}; and for diabetes mellitus, FPG ≥7.0 mmol l^{-1} and/or 2-h PG ≥11.1 mmol l^{-1}.

Definition of cardiovascular events

The outcomes of the present analysis were stroke, coronary heart disease and total CVD events (stroke and coronary heart disease). Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for more than 24 h. Rare causes of cerebrovascular disease, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma or Moyamoya disease, were not considered among the stroke cases. The diagnosis and classification of stroke were based on clinical information, ancillary laboratory examinations (that is, neuroimaging, cerebral angiography, echocardiography or carotid duplex imaging) and autopsy findings.

The criteria for a diagnosis of coronary heart disease included first-ever fatal or non-fatal myocardial infarction, sudden cardiac death within 1 h of the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty. Myocardial infarction was diagnosed when a subject met at least two of following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic ECG changes; or (4) morphologic changes of the heart, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Sudden cardiac death was defined as natural death attributable to cardiac causes, heralded by an abrupt loss of consciousness, within 1 h after onset of acute symptoms.

Statistical analysis

The incidence rates were calculated using the person-year method and adjusted for age by the direct method using 10-year age groupings. Differences in incidence rates between subgroups defined by QTc levels were tested using the Cox proportional hazards model including age. The multivariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) were also estimated using the Cox proportional hazards model. A P-value of <0.05 was considered statistically significant in all analyses. The SAS program (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses.

RESULTS

Mean QTc levels were 403 ms for men and 417 ms for women. The baseline characteristics according to QTc prolongation (>440 ms) are shown separately for men and women in Table 1. In both sexes, the subjects with QTc prolongation were older, were more likely to have had hypertension, ECG abnormalities, dyslipidemia and smoking habit, and had higher systolic blood pressure, heart rate, plasma fasting glucose and serum triglycerides than those without QTc prolongation.

During the 14-year follow-up period, 145 CVD events (stroke, 85 events; coronary heart disease, 73 events) were observed in men and 158 CVD events (stroke, 121 events; coronary heart disease, 51 events) in women. Table 2 shows the age-adjusted incidence rates and multivariate-adjusted HRs for the development of stroke, coronary heart disease and total CVD according to QTc levels among men. The incidence rates of stroke rose progressively with increasing QTc levels, and the highest risk of stroke was observed in the subgroup with QTc levels of ≥440 ms. These relationships remained significant even after controlling for age, hypertension, heart rate, ECG abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, BMI, total and HDL cholesterol, alcohol consumption, smoking habit and regular exercise (P=0.02 for trend). Comparable associations were also observed for coronary heart disease (P=0.001 for trend) and total CVD (P=0.0004 for trend). When non-HDL cholesterol was included in the multivariate model as a covariate instead of total cholesterol, similar results were obtained (P trend=0.02 for stroke, 0.001 for coronary heart disease and 0.0004 for total CVD).

In contrast to men, women showed no clear associations between QTc levels and incidence rates of total and cause-specific CVD (Table 3, P trend=0.23 for stroke, 0.76 for coronary heart disease and 0.58 for total CVD). These associations remained insignificant even after adding non-HDL cholesterol into the multivariate model instead of total cholesterol (P trend>0.2 for all outcomes). Multivariate-adjusted HRs of QT interval prolongation declined as QTc ≥450 ms and ≥460 ms compared with the reference group with QTc < 400 ms were 1.56 (95% CI, 0.76–3.21) and 1.55 (95% CI, 0.68–3.57) for stroke, 1.00 (95% CI, 0.32–3.17) and 1.17 (95% CI, 0.30–4.58) for coronary heart disease, and 1.21 (95% CI, 0.65–2.25) and 1.37 (95% CI, 0.67–2.78) for total CVD. Multivariate-adjusted HRs

Table 1 Baseline characteristics according to QT interval prolongation among men and women

	Men		*Women*	
	QTc <440 ms (n=913)	*QTc ⩾440 ms (n=74)*	*QTc <440 ms (n=1212)*	*QTc ⩾440 ms (n=240)*
Age (years)	56 (11)	68 (13)	57 (11)	65 (13)
Systolic blood pressure (mm Hg)	133 (19)	144 (25)	130 (21)	143 (24)
Diastolic blood pressure (mm Hg)	81 (11)	80 (13)	75 (11)	78 (11)
Hypertension (%)[a]	42	66	34	58
Heart rate (b.p.m.)	64 (10)	67 (13)	6 (9)	72 (11)
ECG abnormalities (%)[b]	18	32	12	19
Plasma fasting glucose (mmol l^{-1})	5.88 (1.21)	6.21 (2.31)	5.66 (1.22)	5.97 (1.68)
Diabetes (%)[c]	14	11	9	13
Impaired glucose tolerance (%)[d]	18	15	17	23
Impaired fasting glycemia (%)[e]	7	13	5	5
Body mass index (kg m^{-2})	22.9 (2.9)	21.2 (3.2)	22.9 (3.2)	22.8 (3.6)
Obesity (%)[f]	24	11	23	25
Total cholesterol (mmol l^{-1})	5.14 (1.05)	4.82 (1.05)	5.56 (1.05)	5.37 (1.11)
HDL cholesterol (mmol l^{-1})	1.26 (0.31)	1.18 (0.30)	1.35 (0.30)	1.25 (0.29)
Triglycerides (mmol l^{-1})	1.63 (1.37)	1.80 (2.15)	1.17(0.64)	1.41 (1.15)
Dyslipidemia (%)[g]	56	61	55	58
Alcohol intake (%)	63	38	9	10
Smoking habit (%)	50	54	6	10
Regular exercise (%)	11	19	9	8

Abbreviations: BMI, body mass index; b.p.m., beats per minute; ECG, electrocardiogram; HDL, high-density lipoprotein; QTc, heart-rate-corrected QT interval.
Values are means (s.d.) or frequencies.
[a]Blood pressure ⩾140/90 mm Hg or current use of antihypertensive agents.
[b]Minnesota codes: 3–1, 4–1, 4–2 or 4–3.
[c]Fasting glucose ⩾7.0 mmol l^{-1}, postprandial blood glucose ⩾11.1 mmol l^{-1} or current use of hypoglycemic agents.
[d]Fasting glucose <7.0 mmol l^{-1}, and 2-h postprandial blood glucose 7.8–11.0 mmol l^{-1}.
[e]Fasting glucose 6.1–6.9 mmol l^{-1}, and 2-h postprandial blood glucose <7.8 mmol l^{-1}.
[f]BMI ⩾25.0 kg m^{-2}.
[g]Total cholesterol ⩾5.68 mmol l^{-1}, HDL cholesterol ⩽1.03 mmol l^{-1} or triglyceride ⩾1.69 mmol l^{-1}.

Table 2 Age-adjusted incidence rate and multivariate-adjusted hazard ratio for development of stroke, coronary heart disease and total cardiovascular disease according to heart-rate-corrected QT interval among men

	QTc (ms)				
	–399 (n=463)	*400–419 (n=303)*	*420–439 (n=147)*	*440– (n=74)*	P *trend*
Stroke					
Number of events/person-years	32/5940	23/3681	17/1565	13/601	
Incidence rate	6.9	7.3	9.4	16.3	0.03
Hazard ratio (95% CI)[a]	1 (reference)	0.97 (0.56–1.69)	1.31 (0.69–2.47)	2.59 (1.25–5.34)	0.02
Coronary heart disease					
Number of events/person-years	27/5961	20/3715	9/1623	17/633	
Incidence rate	5.2	5.8	4.4	26.2	0.0005
Hazard ratio (95% CI)[a]	1 (reference)	0.86 (0.43–1.69)	0.94 (0.41–2.18)	4.50 (2.18–9.27)	0.001
Total cardiovascular disease					
Number of events/person-years	54/5829.5	39/3614	26/1538	26/578	
Incidence rate	10.9	12.1	14.1	39.1	0.0007
Hazard ratio (95% CI)[a]	1 (reference)	0.97 (0.64–1.49)	1.23 (0.75–2.04)	3.09 (1.82–5.25)	0.0004

Abbreviations: QTc, heart-rate-corrected QT interval; 95% CI, 95% confidence interval.
[a]Hazard ratios and *P*-values were adjusted for age, hypertension, heart rate, electrocardiographic abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterol, alcohol consumption, smoking habit and regular exercise.

per 10-ms increase in QTc interval were 1.05 (95% CI, 0.98–1.13) for stroke, 1.03 (95% CI, 0.91–1.17) for coronary heart disease and 1.03 (95% CI, 0.96–1.10) for total CVD among women.

To examine the combined effect of prolonged QTc and other cardiovascular risk factors on CVD incidence, we estimated the age-adjusted HRs of CVD among four groups of male subjects according to the presence or absence of QTc prolongation (>440 ms) and each of the other risk factors (Table 4). Compared with the reference group without QTc prolongation or hypertension, the risk of developing CVD was significantly higher for the groups with either QTc

Table 3 Age-adjusted incidence rate and multivariate-adjusted hazard ratio for development of stroke, coronary heart disease, and total cardiovascular disease according to heart-rate-corrected QT interval among women

	QTc (ms)				
	–399 (n=350)	*400–419 (n=488)*	*420–439 (n=374)*	*440– (n=240)*	P *trend*
Stroke					
Number of events/person-years	16/4664	35/6268	42/4639	28/2732	
Incidence rate	6.6	6.6	9.6	7.7	0.08
Hazard ratio (95% CI)*	1 (reference)	1.40 (0.77–2.54)	1.86 (1.02–3.41)	1.44 (0.75–2.78)	0.23
Coronary heart disease					
Number of events/person-years	11/4676	16/6381	14/4787	10/2856	
Incidence rate	3.1	2.2	3.1	1.9	0.84
Hazard ratio (95% CI)*	1 (reference)	0.81 (0.33–1.97)	1.29 (0.53–3.12)	0.99 (0.37–2.65)	0.76
Total cardiovascular disease					
Number of events/person-years	25/4605	48/6228	51/4609	34/2729	
Incidence rate	8.5	9.3	11.6	8.3	0.37
Hazard ratio (95% CI)*	1 (reference)	1.25 (0.76–2.06)	1.48 (0.89–2.47)	1.15 (0.66–2.02)	0.58

Abbreviations: QTc, heart-rate-corrected QT interval; 95% CI, 95% confidence interval.
*Hazard ratios and *P*-values were adjusted for age, hypertension, heart rate, electrocardiographic abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, body mass index, total and high-density lipoprotein cholesterol, alcohol consumption, smoking habit, and regular exercise.

Table 4 Age-adjusted hazard ratio for development of total cardiovascular disease according to heart-rate-corrected QT interval prolongation and other risk factors among men

Risk factor	*QTc prolongation*	*No. of events/person-years*	*Relative risk (95% CI)*	P *interaction*
Hypertension[a]				
Absent	Absent	48/6660	1 (reference)	0.38
Present	Absent	71/4322	1.88 (1.30–2.72)	
Absent	Present	8/230	2.63 (1.22–5.65)	
Present	Present	18/348	4.51 (2.58–7.89)	
Diabetes[b]				
Absent	Absent	94/9534	1 (reference)	0.72
Present	Absent	25/1448	1.60 (1.03–2.49)	
Absent	Present	22/513	2.56 (1.58–4.15)	
Present	Present	4/66	5.74 (2.11–15.64)	
Obesity[c]				
Absent	Absent	90/8279	1 (reference)	0.69
Present	Absent	29/2703	1.27 (0.83–1.94)	
Absent	Present	22/505	2.42 (1.50–3.92)	
Present	Present	4/73	6.13 (2.25–16.73)	
Dyslipidemia[d]				
Absent	Absent	49/4875	1 (reference)	0.27
Present	Absent	70/6107	1.35 (0.93–1.95)	
Absent	Present	7/239	1.75 (0.79–3.88)	
Present	Present	19/339	4.11 (2.39–7.04)	
Current smoking				
Absent	Absent	58/5514	1 (reference)	0.15
Present	Absent	61/5468	1.23 (0.86–1.77)	
Absent	Present	9/298	1.96 (0.97–3.98)	
Present	Present	17/281	3.74 (2.15–6.50)	

Abbreviations: BMI, body mass index; QTc, heart-rate-corrected QT interval; QTc prolongation, QTc $\geq$440 ms; 95% CI, 95% confidence interval.
[a]Blood pressure $\geq$140/90 mm Hg or current use of antihypertensive agents.
[b]Fasting glucose $\geq$7.0 mmol l^{-1}, postprandial blood glucose $\geq$11.1 mmol l^{-1} or current use of hypoglycemic agents.
[c]BMI $\geq$25.0 kg m^{-2}.
[d]Total cholesterol $\geq$5.68 mmol l^{-1}, high-density lipoprotein cholesterol $\leq$1.03 mmol l^{-1} or triglyceride $\geq$1.69 mmol l^{-1}.

Table 5 Age-adjusted hazard ratio for development of total cardiovascular disease according to heart-rate-corrected QT interval prolongation and the number of other risk factors among men

Number of risk factors[a]	*QTc prolongation*	*No. of events/person-years*	*Relative risk (95% CI)*	*P interaction*
0–1	Absent	34/4338	1 (reference)	0.89
⩾2	Absent	85/6644	1.74 (1.17–2.59)	
0–1	Present	7/225	2.33 (1.02–5.30)	
⩾2	Present	19/354	4.70 (2.65–8.32)	

Abbreviations: QTc, heart-rate-corrected QT interval; QTc prolongation, QTc ⩾440 ms; 95% CI, 95% confidence interval.
[a]Hypertension, diabetes, obesity, dyslipidemia and current smoking.

prolongation or hypertension, and the highest risk was observed for the group with both QTc prolongation and hypertension. Similar associations were observed for combinations of QTc prolongation and every other risk factor (diabetes, obesity, dyslipidemia or current smoking). There were no significant interactions between QTc prolongation and these cardiovascular risk factors (all $P>0.1$ for interaction). The findings obtained from these analyses were substantially unchanged even after controlling for other risk factors in the multivariate analyses. Age-adjusted HRs for the development of total CVD according to the presence or absence of QTc prolongation (>440 ms) and number of risk factors (0–1 *vs.* ⩾2) among men are also shown in Table 5. There were no significant interactions between QTc prolongation and the number of risk factors (P=0.89 for interaction).

DISCUSSION

The present prospective analysis of a community-dwelling Japanese population clearly shows that QTc prolongation on ECG is an independent predictor of stroke, coronary heart disease and total CVD events among men. These associations remained strong even after controlling for age, hypertension, heart rate, ECG abnormalities, diabetes, impaired glucose tolerance, impaired fasting glycemia, BMI, total and HDL cholesterol, alcohol consumption, smoking habit and regular exercise. Furthermore, the effects of QTc were comparable for patients with or without other cardiovascular risk factors such as hypertension, diabetes, obesity, dyslipidemia or current smoking. However, similar associations were not observed for women.

To the best of our knowledge, only two hospital-based prospective studies have reported an association between QT interval prolongation and the risk of stroke.[5,7] QT interval prolongation (QTc ⩾470 ms) was associated with 2.2-fold higher incidence rates of stroke among 471 Brazilian subjects with type 2 diabetes,[5] whereas no clear associations between QT interval prolongation (QTc ⩾440 ms for men and QTc ⩾450 ms for women) and the development of stroke were found among 2110 Italian subjects with essential hypertension.[7] This study is the first to examine this issue in a general population and clearly shows that QT interval prolongation can predict the incidence of stroke among Japanese men.

A few large-scale observational studies have investigated the association between QT interval prolongation and the future risk of coronary heart disease.[3,4,6] The Atherosclerosis Risk in Communities study reported that QT interval prolongation (QTc ⩾440 ms for men and QTc ⩾454 ms for women) was associated with 1.5- to 5.0-fold increased risk of incident coronary heart disease among general populations of white Americans or African Americans.[3] Robbins *et al.*[4] reported that elderly subjects in the United States with QTc intervals >450 ms had higher coronary heart disease mortality than those with QTc intervals <410 ms. The Zutphen study showed that Dutch men with prolonged QTc (⩾440 ms) had 3.3- to 4.3-fold higher risk of death from coronary heart disease.[6] An Adult Health Study of the Radiation Effects Research Foundation showed that elderly Japanese with prolonged QTc (> 440 ms) had a 2.49-fold higher risk of coronary death compared with those with QTc intervals ⩽420 ms.[22] The present analysis from the Hisayama study confirms the results of previous cohort studies and provides more detailed information regarding the effects of QTc prolongation on the risk of future coronary events in Japanese men.

The mechanism underlying the association between QT interval prolongation and CVD has not been clearly defined, but the QT interval has been shown to be related to ventricular hypertrophy.[23] QT interval has also been shown to be associated with subclinical arterial disease.[24–26] Thus, QT interval prolongation, as a marker of ventricular hypertrophy or subclinical arterial disease, may predict future CVD events.

Another important finding from the present analysis is the lack of clear associations between QTc prolongation and CVD among women. This finding was consistent with previous observational studies. Schouten *et al.* have shown that QTc prolongation (⩾440 ms) was associated with 1.8-fold higher mortality rates from CVD among healthy Dutch men, but not among women. The reason for this finding has not been clearly resolved, but it has been suggested that sex hormones attenuate the association between QT interval prolongation and CVD. Estrogen has been reported to prolong the QT interval through downregulation of HERG-encoded potassium channel expression.[27] At the same time, endogenous estrogen has been shown to protect against the development of atherosclerosis.[18,27,28] Such conflicting effects of sex hormones might weaken the association of QT interval with CVD among women. Another possible reason for the sex difference in the risks of CVD might stem from differences in the atherosclerotic process between men and women. Generally, it is considered that atherosclerosis progresses at a faster rate in men than in women. Thus, it may be easier to detect the association between QT interval prolongation and CVD in men.

Several limitations of our study should be discussed. First, our study lacks information on medication use, which could affect the QT interval duration. It is known that several medications, including antiarrhythmic medications, antibiotics, antipsychotic agents or antihistamines can alter QT interval duration. However, these medications were rarely used in Japan in 1988, when the ECGs in our study were performed. This suggests that such a bias did not invalidate the present findings. Second, we have no information on subjects with congenital long-QT syndrome. However, the prevalence of congenital long-QT syndrome has been reported to be <0.1%.[29] Thus, the influence of congenital long-QT syndrome would seem to be negligible. Third, our findings are based on a 1-day measurement of clinical findings such as ECG, blood pressure levels and blood tests, which may not accurately reflect the status of the study participants. Errors in measuring QTc interval, blood pressure levels or blood test results could have weakened the relationships in the present analysis.

However, this source of variability could not account for the relationship observed in this study, because a random misclassification of such a nature would tend to underestimate the study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study.

In conclusion, our study found that QTc prolongation was an independent predictor of stroke and coronary heart disease in a general population of Japanese male subjects. QTc measurement is a low-cost and noninvasive test to detect high-risk males who should receive special attention. Approaches for the prevention of high-risk CVD using QTc measurement are likely to provide additional protection against the burden of CVD among Japanese male subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported in part by Grants-in-Aid for Scientific Research A (No. 18209024) and Scientific Research C (No. 19590633) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Acta Psychiatr Scand 2010: 122: 319–325
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DOI: 10.1111/j.1600-0447.2010.01587.x

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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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Accepted for publication June 16, 2010

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.

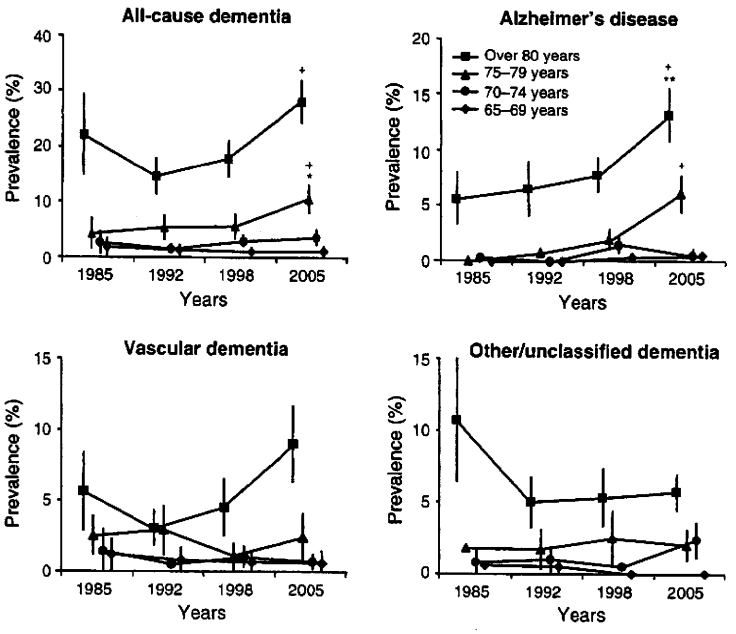

Fig. 1. Secular trends in sex-adjusted prevalence of dementia and its subtypes according to age groups. *P < 0.05, **P < 0.01 vs. 1985, +P for trend < 0.01. The vertical bars of 95% confidence intervals of adjusted prevalence were truncated at zero or more.

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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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.
***Neurology*® 2010;75:764-770**

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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e-Pub ahead of print on August 25, 2010, at www.neurology.org.

From the Departments of Neuropathology (T.M., K.S., K.F., S.O.S., T.I.), Psychiatry (T.M., K.S., K.F., Y.M., A.S., S.K.), and Environmental Medicine (Y.T., J.H., Y.M., A.S., Y.K.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Study funding: Supported by a Grant-in-Aid for Scientists from the Ministry of Health, Labour and Welfare, Japan (H19-nanchi-ippan-006), a Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare (Comprehensive Research on Aging and Health: H20-Choujuu-004), and a Grant-in-Aid for Scientists from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 19300125).

Disclosure: Author disclosures are provided at the end of the article.

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

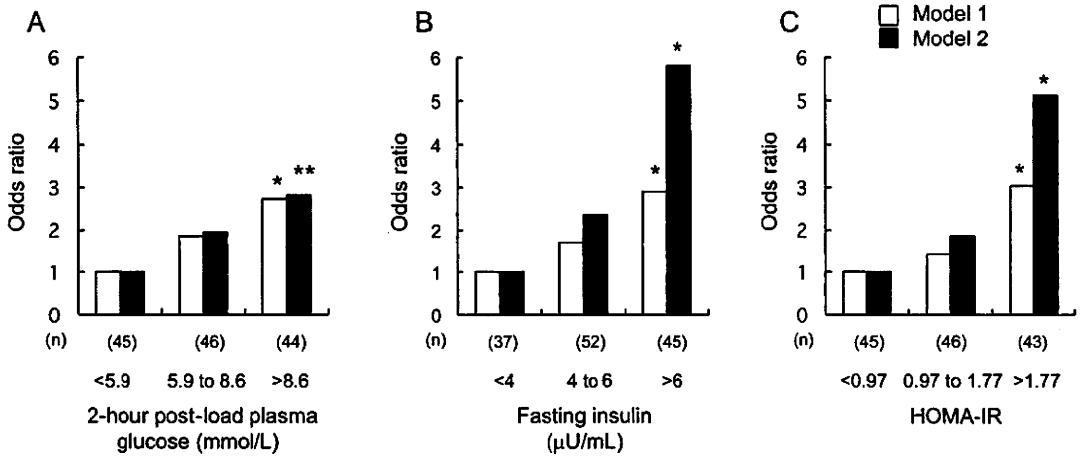
Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; HOMA-IR = homeostasis model assessment of insulin resistance; NP = neuritic plaque; NFT = neurofibrillary tangle; OR = odds ratio.
[a] Model 1: adjusted for age and sex. Model 2: adjusted for 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.

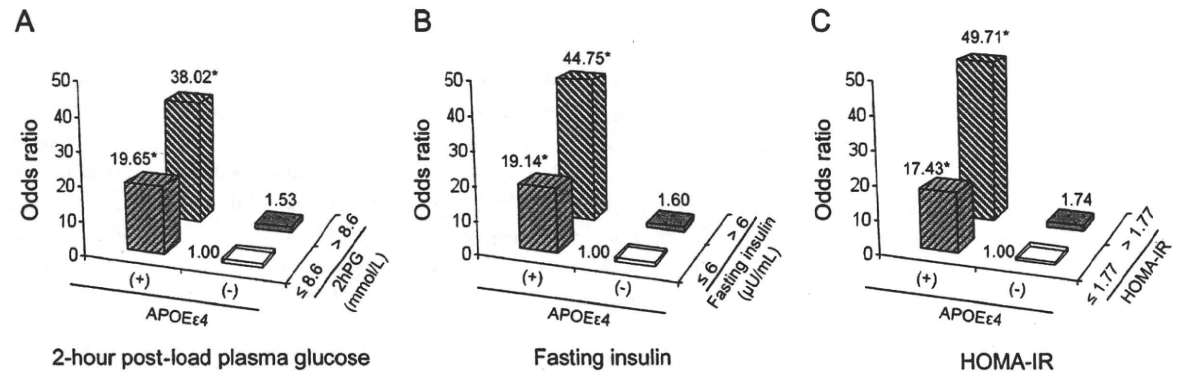
Finally, we examined the combined effects of *APOE* genotype and the magnitude of the diabetes-related factors on the risk of NP pathology (figure 2). For example, the subjects were classified into the following 4 groups according to the 2-hour PG level

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.

ACKNOWLEDGMENT

The authors thank S. Nagae and K. Sato for technical assistance.

DISCLOSURE

Dr. Matsuzaki reports no disclosures. Dr. Sasaki receives research support from the Ministry of Health, Labor and Welfare of Japan. Dr. Tanizaki, Dr. Hata, Dr. Fujimi, Dr. Matsui, Dr. Sekita, and Dr. Suzuki report no disclosures. Dr. Kanba has served on scientific advisory boards for Eli Lilly and Company, GlaxoSmithKline, Pfizer Inc., Mitsubishi Tanabe Pharma Corporation, Ono Pharmaceutical Co. Ltd., Astellas Pharma Inc., Asahi Kasei Corporation, Shionogi & Co., Ltd., and Otsuka Pharmaceutical Co., Ltd.; has served on the editorial boards of *Molecular Psychiatry*, the *Journal of Neuroscience and Psychiatry*, the *Asian Journal of Psychiatry*, and the *Asia Pacific Journal of Psychiatry*; has received speaker honoraria from Eli Lilly and Company, GlaxoSmithKline, Pfizer Inc., Asahi Kasei Corporation, Janssen, Tsumura & Co., Ajinomoto Co., Inc., Mitsubishi Tanabe Pharma Corporation, Meiji Techno Co. Ltd., Kyowa Hakko Kirin Pharma, Inc., Dainippon Sumitomo Pharma Co., Ltd., Organon International (Schering-Plough Corp.), Otsuka Pharmaceutical Co., Ltd., and Astellas Pharma Inc.; and has received research support from Eli Lilly & Co., GlaxoSmithKline, Pfizer Inc., Asahi Kasei Corporation, Janssen, Tsumura & Co., Ajinomoto Co., Inc., Mitsubishi Tanabe Pharma Corporation, Meiji Techno Co. Ltd., Kyowa Hakko Kirin Pharma, Inc., Dainippon Sumitomo Pharma Co., Ltd., Organon International (Schering-Plough Corp.), Otsuka Pharmaceutical Co., Ltd., and the Ministry of Health, Labor and Welfare of Japan and the Ministry of Education, Culture, Sports, Science and Technology of Japan. Dr. Kiyohara receives research support from the Ministry of Health, Labor and Welfare of Japan. Dr. Iwaki receives research support from the Ministry of Education, Culture, Sports, Science and Technology of Japan and serves on the editorial boards of *Neuropathology*, *Brain Tumor Pathology*, *Pathology—Research and Practice*, and *Pathology International*.

Received October 5, 2009. Accepted in final form February 19, 2010.

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