Table 3. Total energy expenditure (TEE) and duration of each activity among groups by physical activity level

	Physical activity level			*P*
	I Sedentary	II Moderately active	III Active	
TEE by DLW (MJ/day)	8.11 (1.39)[a,b]	9.18 (2.29)[b]	10.76 (4.25)	*<0.001*
TEE by questionnaire (MJ/day)	7.78 (1.21)[b,c]	8.45 (2.87)	8.90 (3.06)	0.006
Total METs (METs·h/day)	33.5 (4.1)[b]	34.4 (4.8)[b]	35.8 (6.4)	<0.001
Difference in TEE between DLW and PAQ (MJ/day)	−0.07 (0.50)[b]	−0.80 (1.62)[b]	−2.02 (2.23)	<0.001
Difference in TEE between DLW and PAQ (%)	−0.9 (15.3)[b]	−8.4 (17.6)[b]	−19.1 (19.0)	<0.001
Total duration of physical activity (h/day)				
Light (<3 METs)	3.41 (3.58)	4.14 (3.50)	4.16 (3.72)	0.155
Moderate (3–5.9 METs)	1.65 (1.81)[b]	2.06 (2.07)[b]	2.53 (3.89)	<0.001
Vigorous (≥6 METs)	0.00 (0.09)[b]	0.00 (0.20)[a]	0.0 (0.54)	0.007
Duration of leisure-time physical activity (h/day)				
Light (<3 METs)	0.00 (0.26)	0.00 (0.07)	0.00 (0.09)	0.766
Moderate (3–5.9 METs)	0.01 (0.17)	0.02 (0.23)	0.03 (0.27)	0.965
Vigorous (≥6 METs)	0.00 (0.08)	0.00 (0.02)	0.00 (0.00)	0.556
Duration of work (h/day)				
Sitting	0.00 (2.86)	1.55 (4.61)	0.00 (4.29)	0.129
Standing	1.75 (2.20)	1.42 (2.14)	2.00 (2.85)	0.176
Walking	0.25 (0.86)[b,c]	0.54 (1.90)[b]	1.00 (3.07)	<0.001
Proportion of subjects participating in heavy work (%)	6.1	24	36.1	0.003

TEE: total energy expenditure; DLW: doubly labeled water; MET: metabolic equivalent; PAQ: physical activity questionnaire.
All values are median (interquartile), unless otherwise indicated.
[a]$P < 0.05$ as compared with physical activity level III.
[b]$P < 0.01$ as compared with physical activity level III.
[c]$P < 0.01$ as compared with physical activity level II.

Table 4. Correlation coefficients for physical activity level (as measured by doubly labeled water method) and duration of physical activities

	Correlation coefficient	*P* value	Partial correlation coefficient	*P* value
Total duration of physical activity (h/day)				
Light (<3 METs)	0.034	0.608	0.022	0.746
Moderate (3–5.9 METs)	0.257	<0.001	0.225	0.001
Vigorous (≥6 METs)	0.354	0.481	0.330	<0.001
Duration of leisure-time physical activity (h/day)				
Light (<3 METs)	−0.018	0.790	0.008	0.910
Moderate (3–5.9 METs)	0.002	0.978	0.000	0.996
Vigorous (≥6 METs)	−0.048	0.474	−0.072	0.286
Duration of work (h/day)				
Sitting	−0.064	0.337	−0.133	0.047
Standing	0.165	0.013	0.256	<0.001
Walking	0.271	<0.001	0.239	<0.001
Heavy	0.376	<0.001	0.354	<0.001

MET: metabolic equivalent; TEE: total energy expenditure.
Partial correlation coefficients are adjusted for sex and age group.

subjects at worksites requiring vigorous physical activity (ie, shipbuilding and hospitals). This may explain the higher physical activity level of the subjects.

Neilson et al reviewed a validation study of a physical activity questionnaire and suggested that, at the group level, the mean difference in TEE ranged from −800 to 1589 kcal/day (−3.35 to 6.65 MJ/day) and that the Spearman correlation coefficient for TEE ranged from 0.15 to 0.51.[2] As compared with these results, JALSPAQ showed a smaller negative mean difference of −1.15 MJ/day and a higher correlation (Spearman correlation, 0.742; $P < 0.001$). A comparison of individual-level agreement indicates that the width of the 95% LOA in our study (7.68 MJ/day) was smaller than that in most other questionnaires described in the review of Neilson and colleagues (1133 to 17948 kcal/day; 4.74 to 75.09 MJ/day).[2] The relatively good agreement in this study partly resulted from the greater number of subjects ($n = 226$ in the present study vs $n = 13$ to $n = 65$ in previous studies) and the wide variation in TEE. Standard deviation was 2.77 MJ in the present study and 0.35 to 3.51 MJ in previous studies. A study by Racette showed the lowest 95% LOA (−2.42 to 0.16 MJ/day).[19] However, that study was part of an investigation of a 17-week outpatient weight loss treatment, so the subjects were thought to be highly motivated and to have answered the questionnaire carefully. One reason why TEE is assumed to have greater accuracy than the existing questionnaire is that it is believed to have more detailed questions regarding occupational activity, housework, and leisure-time physical activity.

JALSPAQ tended to greatly underestimate TEE in more active subjects, possibly because the algorithm for the calculation of TEE for JALSPAQ only includes duration of time spent sitting, standing, and walking. These activities were scored on a scale from 1.5 to 4.0 METs. Even when there was a question regarding carrying heavy objects or engaging in activity of similar intensity, such activity was not used to calculate TEE. Thus, underestimation would be greater in subjects who expended considerable energy at work. In the

present study, 16 subjects were engaged in shipbuilding, and the differences between TEE by DLW and JALSPAQ ranged from −10.98 to 0.34 MJ/day; TEE was overestimated by JALSPAQ in only 2 subjects.

Although TEE estimated by JALSPAQ showed a relatively good correlation with TEE by DLW, RMR accounted for a large part of TEE. To lessen the contribution of RMR, PAL was compared between the two methods. The results for PAL were poor, and individual differences were widely distributed. Therefore, JALSPAQ must either be improved or another new questionnaire should be developed to assess individual PAL.

We also attempted to identify a physical activity that characterized physical activity level. Our results showed that total time spent in moderate physical activity was significantly greater in the active group. In addition, moderate and vigorous physical activity had a weak but significant correlation with PAL. Thus, moderate physical activity is an important component of physical activity level, as Westerterp has suggested.[20] However, the duration of moderate physical activity did not differ in the sedentary and moderate groups. Wareham et al used a very brief questionnaire that only included physical activity during work and recreational activities and found that physical activity ratio (daytime energy expenditure/resting metabolic rate), which was estimated using a heart rate monitor, did not differ between inactive and moderately inactive groups, even though VO_{2max} was different between these groups.[21] Another method of classifying physical activity in sedentary subjects should thus be considered.

The present results also suggest that intensity and duration of physical activity during work (including occupational activity and housework) strongly affect PAL, whereas leisure-time physical activity does not. Both work and leisure-time physical activity play fundamental roles in total physical activity, which explains why previous brief physical activity questionnaires assessed only physical activity during work and leisure time.[21,22] In the present study, because the mean duration of all leisure-time physical activity was 22 ± 21 minutes per day, the effect of leisure-time physical activity on TEE might be very small.

The most significant limitation of this study was that subjects were not selected randomly: they joined the study as volunteers. Hence, as compared with the general population, they might have remembered their physical activities better and completed the questionnaire more carefully. In addition, the variation in their physical activity level might differ from that of the general Japanese population. However, we were unable not determine the nature or extent of error that resulted from these subject characteristics. A second limitation is that the study periods for DLW and JALSPAQ were not identical. The DLW method determined the average TEE over 1 or 2 weeks. In contrast, JALSPAQ assessed typical physical activity over 1 month. This discrepancy could affect the validation of JALSPAQ. Finally, the relatively small proportion of sedentary subjects made it difficult to characterize the sedentary population. Although we tried to collect subjects with a broad range of physical activities, we could not collect comparable numbers of sedentary and active subjects.

In conclusion, PAL by JALSPAQ weakly correlated with PAL by DLW, although TEE by JALSPAQ was better correlated with TEE by DLW than with TEE assessed by the questionnaires used in previous studies. TEE underestimation was greater in active subjects than in sedentary and moderately active subjects. In addition, in this population, total moderate physical activity and physical activity during work were related to physical activity level, whereas leisure-time physical activity was not. To improve the physical activity questionnaire, an algorithm for heavy work should be added.[4] In addition, to better differentiate sedentary subjects form moderate subjects, additional questionnaire items should be added or the algorithm should be reevaluated.

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Glucose tolerance status and risk of dementia in the community

The Hisayama Study

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ABSTRACT

Objective: We investigated the association between glucose tolerance status defined by a 75-g oral glucose tolerance test (OGTT) and the development of dementia.

Methods: A total of 1,017 community-dwelling dementia-free subjects aged ≥60 years who underwent the OGTT were followed up for 15 years. Outcome measure was clinically diagnosed dementia.

Results: The age- and sex-adjusted incidence of all-cause dementia, Alzheimer disease (AD), and vascular dementia (VaD) were significantly higher in subjects with diabetes than in those with normal glucose tolerance. These associations remained robust even after adjustment for confounding factors for all-cause dementia and AD, but not for VaD (all-cause dementia: adjusted hazard ratio [HR] = 1.74, 95% confidence interval [CI] = 1.19 to 2.53, $p = 0.004$; AD: adjusted HR = 2.05, 95% CI = 1.18 to 3.57, $p = 0.01$; VaD: adjusted HR = 1.82, 95% CI = 0.89 to 3.71, $p = 0.09$). Moreover, the risks of developing all-cause dementia, AD, and VaD significantly increased with elevated 2-hour postload glucose (PG) levels even after adjustment for covariates, but no such associations were observed for fasting plasma glucose (FPG) levels: compared with those with 2-hour PG levels of <6.7 mmol/L, the multivariable-adjusted HRs of all-cause dementia and AD significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L or over, and the risk of VaD was significantly higher in subjects with levels of ≥11.1 mmol/L.

Conclusions: Our findings suggest that diabetes is a significant risk factor for all-cause dementia, AD, and probably VaD. Moreover, 2-hour PG levels, but not FPG levels, are closely associated with increased risk of all-cause dementia, AD, and VaD. *Neurology*® 2011;77:1126–1134

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised; **FPG** = fasting plasma glucose; **HR** = hazard ratio; **IFG** = impaired fasting glycemia; **IGT** = impaired glucose tolerance; **NGT** = normal glucose tolerance; **OGTT** = oral glucose tolerance test; **PG** = postload glucose; **VaD** = vascular dementia.

Diabetes mellitus is one of the most common metabolic disorders, and its prevalence has risen globally in recent years. Some epidemiologic studies have reported that diabetes is independently implicated in the development of dementia.[1–3] However, these findings are inconsistent for its subtypes; one study found an association between diabetes and the risk of both Alzheimer disease (AD) and vascular dementia (VaD),[1] whereas other studies found an association with only AD[2,3] or only VaD,[4–7] and still others showed no association between diabetes and either condition.[8,9] These conflicting results may have been related to differences in the study designs, including the defined criteria for diabetes and dementia subtypes, as well as in the regional characteristics and ethnicities of the settings and subjects. Thus, accurate definitions of diabetes and dementia subtypes are needed to ascertain the true associations between the two, and a 75-g oral glucose tolerance test (OGTT) and morphologic examination of the brain may meet this requirement. However, to date, very few cohort studies have had enough quality data to allow reliable diagnosis using these methods.

Supplemental data at www.neurology.org

Supplemental Data

From the Departments of Environmental Medicine (T.O., Y.D., T.N., Y.H., J.H., Y.K.), Neuropsychiatry (T.O., S.K.), Medicine and Clinical Science (Y.D., T.N., Y.H., J.H.), and Neuropathology (T.I.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

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To resolve these issues, we performed a prospective cohort study of dementia in a Japanese community-dwelling population, all members of which underwent the OGTT. The most important feature of this study is that the subtypes of dementia were verified by detailed neurologic and morphologic examination, including neuroimaging and autopsy. Using data from this cohort study, we investigated the association between glucose tolerance levels defined by the OGTT and the development of dementia and its subtypes.

METHODS

Study population. A population-based prospective study of cerebro-cardiovascular diseases was begun in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island in Japan. In addition, comprehensive surveys of cognitive impairment in the elderly of this town have been conducted since 1985. In 1988, a total of 1,228 residents aged ≥60 years (91.1% of the total population in this age group) participated in a screening examination for the present study. After exclusion of 33 subjects who had dementia, 90 who had already had breakfast, 5 who were on insulin therapy, and 81 who could not complete the OGTT, a total of 1,019 subjects without dementia underwent the OGTT. From a total of 1,019 subjects, 2 who died before starting follow-up were excluded, and the remaining 1,017 subjects (437 men and 580 women) were enrolled in this study.

Follow-up survey. The subjects were followed up prospectively for 15 years, from December 1988 to November 2003 (mean 10.9 years; SD 4.1 years). A complete description of the follow-up survey is provided in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Diagnosis of dementia. The diagnosis of dementia was made based on the guidelines of the *DSM-III-R*.[10] Subjects diagnosed with AD met the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[11] and subjects diagnosed with VaD met the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.[12] Possible or probable dementia subtypes were diagnosed with clinical information including neuroimaging. Definite dementia subtypes were also determined on the basis of clinical and neuropathologic information. The diagnostic procedure for autopsy cases was reported previously.[13] A neuropathologic diagnosis of AD was made following the National Institute on Aging–Reagan Institute criteria,[14] where the frequency of neuritic plaques and neurofibrillary tangles was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease criteria[15] and Braak stage.[16] Definite VaD cases were confirmed with causative stroke or cerebrovascular change and no neuropathologic evidence of other forms of dementia. Every dementia case was adjudicated by expert psychiatrists.

During the follow-up, 232 subjects (79 men and 153 women) developed dementia. Of these, 201 (86.6%) were evaluated by brain imaging, and 118 (50.9%) underwent brain autopsy; in 110, both were performed. Thus, 209 subjects in all (90.1%) had some kind of morphologic examination. Among the 118 autopsy cases, the clinical diagnosis of 42 cases (35.6%) was changed by the neuropathologic findings. Among all dementia cases, 18 AD cases and 11 VaD cases had other coexisting subtypes of dementia. These cases were counted as events in the analysis for other dementia. In all, 105 cases were categorized as AD, 65 as VaD, and 62 as other dementia.

Risk factor measurement. At the baseline examination, we performed the OGTT after an at least 12-hour overnight fast. Plasma glucose levels were determined by the glucose-oxidase method. Glucose tolerance status was defined by the 1998 WHO criteria[17]: normal glucose tolerance (NGT), fasting plasma glucose (FPG) <6.1 and 2-hour postload glucose (PG) <7.8; impaired fasting glycemia (IFG), FPG 6.1 to 6.9 and 2-hour PG <7.8; impaired glucose tolerance (IGT), FPG <7.0 and 2-hour PG 7.8 to 11.0; and diabetes, FPG ≥7.0 mmol/L or 2-hour PG ≥11.1 mmol/L. Each of the FPG and 2-hour PG level was also divided into 4 categories (FPG: <5.6, 5.6 to 6.0, 6.1 to 6.9, and ≥7.0 mmol/L; 2-hour PG: <6.7, 6.7 to 7.7, 7.8 to 11.0, and ≥11.1 mmol/L).

In order to assess the independent effects of glucose tolerance levels on dementia occurrence, the following baseline factors in addition to age and sex were used as confounding factors: 1) information on smoking habits, alcohol intake, and physical activity was obtained by means of a questionnaire administered to each subject; 2) a low education level was defined as ≤6 years of formal education; 3) history of stroke was determined on the basis of all clinical data available in the Hisayama Study; 4) hypertension was defined as blood pressure levels ≥140/90 mm Hg or current treatment with antihypertensive agents; 5) EKG abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, or 3) or atrial fibrillation (8-3); 6) serum total cholesterol levels were measured enzymatically; and 7) body mass index (kg/m^2) and waist to hip ratio were used as indicators of obesity.

Statistical analysis. The SAS software package, version 9.2 (SAS Institute, Cary, NC), was used to perform all statistical analyses. Age- and sex-adjusted mean values of possible risk factors were calculated by the analysis of covariance method. Frequencies of risk factors were adjusted for age and sex by the direct method. The differences in the mean values and frequencies of risk factors between NGT and other glucose tolerance levels were tested using Fisher least significant difference method and logistic regression analysis, respectively. The incidence of dementia was calculated by the person-years method and was adjusted for age and sex by the direct method using 5-year age groups of the overall study population; the differences among glucose tolerance levels and trends across FPG and 2-hour PG levels were tested using Cox proportional hazards model. The adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were also calculated using the Cox proportional hazards model. Missing values of waist to hip ratio (n = 27) and education (n = 12) were replaced with the means in the multivariate analysis. The population attributable fraction of combined category of IGT and diabetes for dementia was calculated using the following equation with the observed multivariate-adjusted HR of the combined category and its frequency in event cases (Pe)[18]:

$$PAF = Pe\,(HR - 1)/HR$$

Two-sided $p < 0.05$ was considered statistically significant in all analyses.

Standard protocol approvals, registrations, and patient consents. This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Re-

Table 1 Age- and sex-adjusted mean values or frequencies of potential risk factors for dementia according to the 1998 WHO criteria: The Hisayama Study, 1988[a]

	Normal glucose tolerance (n = 559)	Impaired fasting glycemia (n = 73)	Impaired glucose tolerance (n = 235)	Diabetes (n = 150)	No. of missing values
Age, y, mean (SD)	68 (6)	70 (6)[b]	69 (6)	69 (6)	0
Men, %	40.8	52.1	43.8	45.3	0
Fasting plasma glucose, mmol/L, mean (SD)	5.3 (0.9)	6.4 (0.9)[c]	5.8 (0.9)[c]	7.7 (0.9)[c]	0
Two-hour postload glucose, mmol/L, mean (SD)	5.9 (2.2)	5.9 (2.2)	8.9 (2.2)[c]	14.9 (2.2)[c]	0
Systolic blood pressure, mm Hg, mean (SD)	133 (21)	141 (21)[c]	143 (21)[c]	145 (21)[c]	0
Diastolic blood pressure, mm Hg, mean (SD)	75 (10)	76 (10)	78 (10)[c]	77 (10)[b]	0
Hypertension, %[d]	43.8	66.7[c]	63.2[c]	62.2[c]	0
Electrocardiogram abnormalities, %	20.6	31.7	18.8	21.6	0
Body mass index, kg/m^2, mean (SD)	21.8 (3.0)	22.2 (3.0)	23.2 (3.0)[c]	23.2 (3.0)[c]	0
Waist to hip ratio, cm/cm, mean (SD)	0.91 (0.07)	0.93 (0.07)[b]	0.93 (0.07)[c]	0.94 (0.07)[c]	27
Total cholesterol, mmol/L, mean (SD)	5.3 (1.1)	5.5 (1.1)	5.4 (1.1)	5.7 (1.1)[c]	0
History of stroke at entry, %	3.3	3.5	5.9	6.3	0
Education ≤6 y, %	10.3	12.5	13.9	11.3	12
Smoking, %	23.5	23.8	23.5	22.7	0
Alcohol intake, %	23.4	29.0	27.7	34.8[c]	0
Physical activity, %	20.2	22.8	16.8	14.7	0

[a] Mean age was sex adjusted. Percentage of men was age adjusted. Electrocardiogram abnormalities were defined as Minnesota Code 3-1, 4-1, 4-2, 4-3, or 8-3.
[b] $p < 0.05$ vs normal glucose tolerance.
[c] $p < 0.01$ vs normal glucose tolerance.
[d] Hypertension: blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.

search, and written informed consent was obtained from the participants.

RESULTS Table 1 shows the age- and sex-adjusted mean values or frequencies of risk factors for dementia by the WHO criteria at baseline. Compared with those with NGT, the mean values of systolic and diastolic blood pressures, body mass index, waist to hip ratio, and total cholesterol, and the frequencies of hypertension and alcohol intake, were higher in subjects with IFG, IGT; or diabetes.

The age- and sex-adjusted incidences and adjusted HRs of all-cause dementia and its subtypes according to glucose tolerance status defined by the WHO criteria are shown in table 2. Compared with those with NGT, the age- and sex-adjusted incidence and HR of all-cause dementia were significantly higher in subjects with IGT as well as those with diabetes. This association remained unchanged in subjects with diabetes even after adjustment for age, sex, hypertension, EKG abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity. In regard to subtypes of dementia, the age- and sex-adjusted incidence and adjusted HRs of AD were significantly higher in subjects with diabetes than in those with NGT. The age- and sex-adjusted incidence and HR of VaD were significantly increased in subjects with IGT or diabetes compared with those with NGT; however, these associations were not significant after multivariable adjustment. No significant associations were observed between glucose tolerance levels and the risk of other dementia. When IGT and diabetes were brought together in one category, this category also had the significantly higher risks of all-cause dementia, AD, and VaD in the age- and sex-adjusted analysis, and these associations remained significant for all-cause dementia and AD even after adjustment for other possible risk factors. The population attributable fraction of this combined category was 14.6% for all-cause dementia, 20.1% for AD, and 17.0% for VaD.

Table 3 presents the associations between FPG levels and adjusted risks of all-cause dementia and its subtypes. The age- and sex-adjusted incidences and HRs of all-cause dementia and any of the dementia subtypes did not differ among FPG levels. This tendency was unchanged even in the multivariate analysis. Conversely, as shown in table 4, the age- and

Table 2 Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to glucose tolerance status defined by WHO criteria

Glucose tolerance level	Person-years at risk, n	No. of events, n	Age- and sex-adjusted incidence	Crude HR (95% CI)	p	Age- and sex-adjusted HR (95% CI)	p	Multivariable-adjusted[a] HR (95% CI)	p
All-cause dementia									
Normal	6,658	115	20.1	1 (referent)		1 (referent)		1 (referent)	
IFG	854	13	16.0	0.89 (0.50–1.58)	0.70	0.74 (0.42–1.31)	0.30	0.63 (0.35–1.13)	0.12
IGT	2,611	63	24.9	1.46 (1.07–1.99)	0.02	1.40 (1.03–1.91)	0.03	1.35 (0.98–1.86)	0.07
DM	1,544	41	29.3	1.62 (1.14–2.32)	0.008	1.71 (1.19–2.44)	0.003	1.74 (1.19–2.53)	0.004
IGT + DM	4,155	104	26.3	1.52 (1.17–1.98)	0.002	1.51 (1.16–1.97)	0.002	1.46 (1.10–1.92)	0.008
Alzheimer disease									
Normal	6,658	51	8.6	1 (referent)		1 (referent)		1 (referent)	
IFG	854	5	6.6	0.77 (0.31–1.94)	0.58	0.63 (0.25–1.57)	0.32	0.61 (0.24–1.55)	0.29
IGT	2,611	29	11.7	1.53 (0.97–2.41)	0.07	1.46 (0.92–2.30)	0.11	1.60 (0.99–2.59)	0.05
DM	1,544	20	14.2	1.81 (1.08–3.03)	0.03	1.94 (1.16–3.26)	0.01	2.05 (1.18–3.57)	0.01
IGT + DM	4,155	49	12.5	1.63 (1.10–2.41)	0.01	1.62 (1.10–2.40)	0.02	1.73 (1.15–2.60)	0.009
Vascular dementia									
Normal	6,658	27	5.1	1 (referent)		1 (referent)		1 (referent)	
IFG	854	6	7.1	1.76 (0.73–4.26)	0.21	1.40 (0.58–3.41)	0.46	1.01 (0.41–2.52)	0.98
IGT	2,611	20	7.8	1.95 (1.09–3.47)	0.02	1.86 (1.05–3.32)	0.04	1.39 (0.76–2.54)	0.29
DM	1,544	12	8.7	2.00 (1.01–3.95)	0.04	2.07 (1.05–4.09)	0.04	1.82 (0.89–3.71)	0.09
IGT + DM	4,155	32	7.9	1.97 (1.18–3.29)	0.01	1.94 (1.16–3.23)	0.01	1.54 (0.90–2.63)	0.11
Other dementia									
Normal	6,658	37	6.4	1 (referent)		1 (referent)		1 (referent)	
IFG	854	2	2.2	0.42 (0.10–1.75)	0.23	0.36 (0.09–1.51)	0.16	0.34 (0.08–1.44)	0.14
IGT	2,611	14	5.5	0.99 (0.54–1.84)	0.99	0.96 (0.52–1.78)	0.90	0.94 (0.49–1.78)	0.84
DM	1,544	9	6.5	1.08 (0.52–2.24)	0.83	1.10 (0.53–2.28)	0.80	1.19 (0.56–2.52)	0.66
IGT + DM	4,155	23	5.8	1.03 (0.61–1.73)	0.92	1.01 (0.60–1.70)	0.97	0.97 (0.57–1.67)	0.91

Abbreviations: CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; IFG = impaired fasting glycemia; IGT = impaired glucose tolerance.

[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

sex-adjusted incidences and HRs of all-cause dementia, AD, and VaD significantly increased with rising 2-hour PG levels. Compared with those with 2-hour PG levels of <6.7 mmol/L, the age- and sex-adjusted incidences and HRs of all-cause dementia, AD, and VaD were marginally or significantly higher in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L and significantly higher in subjects with 2-hour PG levels of ≥11.1 mmol/L. These associations remained robust even after multivariable adjustment; the risks of all-cause dementia and AD were significantly increased in subjects with 2-hour PG levels of 7.8 to 11.0 mmol/L and over, and the risk of VaD was significantly higher in those with 2-hour PG levels of ≥11.1 mmol/L.

Sensitivity analysis in which only definite cases of dementia determined by brain autopsy were used as event cases did not make any material difference in these findings, except with respect to VaD, for which the significant association disappeared, probably due to the few event cases (table 5). When only clinical diagnoses were used for cases with both clinical and neuropathologic diagnoses, the findings were substantially unchanged, though the HRs became slightly lower probably due to the decreased accuracy of diagnosis (tables e-1, e-2, and e-3).

DISCUSSION In a long-term prospective study of an elderly Japanese population, we demonstrated that diabetes that was assessed 15 years earlier was a significant risk factor for the development of all-cause dementia, AD, and VaD. Moreover, the risks of developing all-cause dementia and its sub-

Table 3 Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to fasting plasma glucose levels

Fasting plasma glucose levels	Person-years at risk, n	No. of events, n	Age- and sex-adjusted incidence	Crude HR (95% CI)	p	Age- and sex-adjusted HR (95% CI)	p	Multivariable-adjusted[a] HR (95% CI)	p
All-cause dementia									
<5.6	5,589	101	20.7	1 (referent)		1 (referent)		1 (referent)	
5.6–6.0	3,286	71	25.1	1.24 (0.91–1.68)	0.17	1.21 (0.89–1.64)	0.22	1.18 (0.86–1.61)	0.31
6.1–6.9	1,724	39	21.6	1.13 (0.91–1.91)	0.14	1.13 (0.78–1.64)	0.52	0.96 (0.65–1.41)	0.82
≥7.0	1,067	21	22.3	1.21 (0.70–1.79)	0.64	1.14 (0.71–1.82)	0.60	1.21 (0.75–1.96)	0.44
				p for trend: 0.23		*p* for trend: 0.42		*p* for trend: 0.63	
Alzheimer disease									
<5.6	5,589	48	10.1	1 (referent)		1 (referent)		1 (referent)	
5.6–6.0	3,286	30	10.3	1.11 (0.70–1.74)	0.67	1.14 (0.72–1.80)	0.58	1.11 (0.69–1.77)	0.68
6.1–6.9	1,724	16	9.1	1.15 (0.65–2.02)	0.64	1.00 (0.57–1.77)	0.99	0.99 (0.49–1.64)	0.72
≥7.0	1,067	11	11.9	1.23 (0.64–2.37)	0.53	1.29 (0.67–2.48)	0.45	1.41 (0.72–2.76)	0.32
				p for trend: 0.47		*p* for trend: 0.56		*p* for trend: 0.58	
Vascular dementia									
<5.6	5,589	24	4.9	1 (referent)		1 (referent)		1 (referent)	
5.6–6.0	3,286	19	6.7	1.38 (0.76–2.52)	0.29	1.29 (0.71–2.36)	0.41	1.19 (0.64–2.19)	0.58
6.1–6.9	1,724	17	8.7	2.40 (1.29–4.47)	0.006	1.93 (1.03–3.61)	0.04	1.48 (0.77–2.84)	0.24
≥7.0	1,067	5	5.2	1.12 (0.43–2.93)	0.82	1.10 (0.42–2.89)	0.84	0.99 (0.37–2.69)	0.99
				p for trend: 0.10		*p* for trend: 0.19		*p* for trend: 0.49	
Other dementia									
<5.6	5,589	29	5.7	1 (referent)		1 (referent)		1 (referent)	
5.6–6.0	3,286	22	8.1	1.33 (0.76–2.31)	0.32	1.27 (0.73–2.21)	0.40	1.21 (0.68–2.16)	0.51
6.1–6.9	1,724	6	3.8	0.69 (0.29–1.67)	0.42	0.60 (0.25–1.45)	0.26	0.53 (0.22–1.31)	0.17
≥7.0	1,067	5	5.2	0.92 (0.36–2.37)	0.86	0.91 (0.35–2.36)	0.85	1.02 (0.39–2.67)	0.97
				p for trend: 0.68		*p* for trend: 0.53		*p* for trend: 0.52	

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

types progressively increased with elevating 2-hour PG levels.

In prior prospective epidemiologic studies, there have been conflicting results regarding the associations between diabetes and incidences of all-cause dementia and AD, while the influence of diabetes on the risk of VaD has been positive in most studies.[1,4–7] Cohort studies in which diabetes was defined by nonfasting blood glucose levels or clinical information did not reveal clear associations of diabetes with the development of all-cause dementia and AD,[4–8] while the risks of dementia and its subtypes significantly increased in diabetes in some studies, most of which defined diabetes using the OGTT.[1–3] The latter findings were in accord with ours. This fact suggests that differences in the methods used to define diabetes lead to a discrepancy in the association between diabetes and the risk of dementia, especially AD, and that an OGTT is essential for the definition of diabetes in epidemiologic studies on the diabetes–dementia association.

In our study, the incidence of VaD was significantly higher in subjects with IGT or diabetes than in those with NGT, but this association disappeared after adjustment for other covariates. This might occur due to the few VaD cases. In addition, since other known cardiovascular risk factors, such as hypertension, obesity, and dyslipidemia, accumulate under a prediabetic or diabetic state, as shown in our data (table 1), IGT and diabetes seem to increase the risk of VaD through mediation of these risk factors, especially hypertension.

In the present study, increased 2-hour PG levels including a prediabetic range were significantly

Table 4 Age- and sex-adjusted incidence and adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes according to 2-hour postload glucose levels

2-Hour postload glucose levels	Person-years at risk, n	No. of events, n	Age- and sex-adjusted incidence	Crude HR (95% CI)	p	Age- and sex-adjusted HR (95% CI)	p	Multivariable-adjusted[a] HR (95% CI)	p
All-cause dementia									
<6.7	5,354	85	17.6	1 (referent)		1 (referent)		1 (referent)	
6.7–7.7	2,277	44	20.9	1.20 (0.84–1.73)	0.32	1.25 (0.87–1.80)	0.24	1.16 (0.78–1.71)	0.47
7.8–11.0	2,844	67	24.7	1.53 (1.11–2.11)	0.009	1.54 (1.12–2.12)	0.009	1.50 (1.07–2.11)	0.02
≥11.1	1,192	36	32.8	2.08 (1.41–3.07)	<0.001	2.32 (1.57–3.44)	<0.001	2.47 (1.62–3.77)	<0.001
				p for trend: <0.001		*p* for trend: <0.001		*p* for trend: <0.001	
Alzheimer disease									
<6.7	5,354	37	7.6	1 (referent)		1 (referent)		1 (referent)	
6.7–7.7	2,277	20	8.8	1.25 (0.73–2.16)	0.41	1.23 (0.71–2.12)	0.46	1.49 (0.83–2.67)	0.17
7.8–11.0	2,844	30	11.3	1.59 (0.98–2.57)	0.06	1.56 (0.96–2.53)	0.07	1.87 (1.13–3.12)	0.02
≥11.1	1,192	18	15.8	2.44 (1.39–4.29)	0.002	2.75 (1.56–4.85)	<0.001	3.42 (1.83–6.40)	<0.001
				p for trend: 0.002		*p* for trend: <0.001		*p* for trend: <0.001	
Vascular dementia									
<6.7	5,354	21	4.6	1 (referent)		1 (referent)		1 (referent)	
6.7–7.7	2,277	12	6.3	1.33 (0.65–2.70)	0.43	1.49 (0.73–3.04)	0.27	1.14 (0.54–2.41)	0.73
7.8–11.0	2,844	20	7.2	1.83 (0.99–3.38)	0.05	1.87 (1.01–3.45)	0.04	1.38 (0.72–2.64)	0.34
≥11.1	1,192	12	11.2	2.75 (1.35–5.60)	0.005	3.15 (1.55–6.43)	0.002	2.66 (1.24–5.70)	0.01
				p for trend: 0.004		*p* for trend: 0.002		*p* for trend: 0.02	
Other dementia									
<6.7	5,354	27	5.4	1 (referent)		1 (referent)		1 (referent)	
6.7–7.7	2,277	12	5.8	1.04 (0.52–2.04)	0.92	1.08 (0.55–2.15)	0.82	0.86 (0.40–1.84)	0.70
7.8–11.0	2,844	17	6.2	1.21 (0.66–2.23)	0.53	1.21 (0.66–2.23)	0.53	1.14 (0.60–2.16)	0.69
≥11.1	1,192	6	5.8	1.05 (0.44–2.55)	0.91	1.12 (0.46–2.71)	0.81	1.21 (0.48–3.04)	0.69
				p for trend: 0.65		*p* for trend: 0.59		*p* for trend: 0.59	

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Multivariate adjustment was made for age, sex, hypertension, electrocardiogram abnormalities, body mass index, waist to hip ratio, total cholesterol, history of stroke at entry, education, smoking habits, alcohol intake, and physical activity.

linked to elevated risks of all-cause dementia, AD, and VaD, but no such associations were observed for FPG. The epidemiologic evidence from Asia has also indicated that 2-hour PG levels are better in detecting prediabetes and diabetes compared with FPG levels.[19] However, very few prospective studies have investigated the associations between FPG as well as 2-hour PG levels and the risks of dementia and its subtypes. Only the Uppsala Longitudinal Study of Adult Men evaluated the associations of FPG levels with the risks of developing AD and VaD,[20,21] and this study concluded that increased FPG levels were not risk factors for these subtypes of dementia. This is in good agreement with our findings. The Uppsala Study[21] and the Honolulu-Asia Aging Study[1] also found no clear associations between 2-hour PG levels and the risks of AD and VaD. These findings are inconsistent with ours. Our recent clinicopathologic study of deceased Hisayama residents revealed that higher levels of 2-hour PG but not of FPG were clearly associated with increased risk for formation of neuritic plaques even after adjustment for confounding factors.[22] This evidence together with the findings of the present study suggests that elevated 2-hour PG levels play an important role in the formation of neuritic plaques, and thereby in the development of AD. Meanwhile, it is well known that increased 2-hour PG levels are closely associated with the development of stroke, which is well established as a main cause of VaD. Thus, it is reasonable to postulate a close association between 2-hour PG levels and the risk of VaD.

Possible pathophysiologic mechanisms through which diabetes or elevated blood glucose levels might

Table 5 Age- and sex-adjusted hazard ratios and their 95% confidence intervals for the development of all-cause dementia and its subtypes determined by autopsy according to 2-hour postload glucose levels

2-Hour postload glucose levels	Person-years at risk, n	No. of events, n	Crude HR (95% CI)	p	Age- and sex-adjusted HR (95% CI)	p
All-cause dementia						
<6.7	5,354	47	1 (referent)		1 (referent)	
6.7–7.7	2,277	23	1.14 (0.69–1.88)	0.61	1.24 (0.75–2.05)	0.39
7.8–11.0	2,844	29	1.19 (0.75–1.89)	0.47	1.20 (0.76–1.91)	0.44
≥11.1	1,192	19	1.94 (1.14–3.31)	0.01	2.24 (1.31–3.83)	0.003
			p for trend: 0.04		*p* for trend: 0.02	
Alzheimer disease						
<6.7	5,354	12	1 (referent)		1 (referent)	
6.7–7.7	2,277	7	1.35 (0.53–3.44)	0.53	1.40 (0.55–3.56)	0.48
7.8–11.0	2,844	12	1.94 (0.87–4.33)	0.10	1.92 (0.86–4.26)	0.11
≥11.1	1,225	8	3.27 (1.34–8.00)	0.009	3.88 (1.58–9.53)	0.003
			p for trend: 0.009		*p* for trend: 0.005	
Vascular dementia						
<6.7	5,354	17	1 (referent)		1 (referent)	
6.7–7.7	2,277	8	1.09 (0.47–2.54)	0.83	1.23 (0.53–2.86)	0.63
7.8–11.0	2,844	8	0.90 (0.39–2.09)	0.81	0.92 (0.40–2.12)	0.84
≥11.1	1,192	7	1.98 (0.82–4.77)	0.13	2.32 (0.96–5.61)	0.06
			p for trend: 0.36		*p* for trend: 0.26	
Other dementia						
<6.7	5,354	18	1 (referent)		1 (referent)	
6.7–7.7	2,277	8	1.04 (0.45–2.39)	0.93	1.17 (0.51–2.70)	0.72
7.8–11.0	2,844	9	0.96 (0.43–2.14)	0.92	0.98 (0.44–2.19)	0.97
≥11.1	1,192	4	1.04 (0.35–3.07)	0.95	1.16 (0.39–3.43)	0.79
			p for trend: 0.99		*p* for trend: 0.88	

Abbreviations: CI = confidence interval; HR = hazard ratio.

affect the initiation and promotion of dementia have been extensively discussed in a number of studies.[23] A recent review summarized 4 major pathways for hyperglycemia-induced dementia: namely, atherosclerosis, microvascular disease, glucose toxicity leading to the accumulation of advanced protein glycation and increased oxidative stress, and changes in insulin metabolism resulting in an insulin-resistant state and distorted amyloid metabolism in the brain.[23] The former 2 pathways are considered to be involved in the development of VaD, while the latter 2 pathways may mainly contribute to the development of AD. Additionally, recent evidence has emerged to imply that vascular factors may be involved in AD.[23] It is reported that 2-hour PG values can be a good marker of oxidative stress levels arising from hyperglycemia[24,25] and correlate with insulin resistance.[26] Higher oxidative stress and insulin resistance may precede the accumulation of amyloid-β peptide and neurofibrillary tangles[23,27] and accelerate arteriosclerosis in the brain,[28] resulting in increased risk of AD and VaD. It is known that Asians have lower levels of insulin secretion compared with other ethnic groups[29] and can develop diabetes, insulin resistance, and metabolic syndrome with lower body mass index levels.[30] These findings suggest that hyperglycemia plays a larger role in the development of dementia compared with insulin resistance in Asians including Japanese. Further studies are needed to elucidate the pathogenesis of hyperglycemia and diabetes in the development of dementia.

The strengths of our study include its longitudinal population-based study design, use of OGTT for determination of glucose tolerance levels in all subjects, long duration of follow-up, perfect follow-up of subjects, and morphologic examination of the brains of most dementia cases with autopsy and neuroimaging. Several limitations of our study should be noted. First, the diagnosis of glucose tolerance status was based on a single measurement of glucose levels at baseline, as was the case in most other epidemiologic studies. During the follow-up, risk factor levels were changed due to modifications in lifestyle or medication especially in subjects with diabetes, and

misclassification of glucose tolerance categories was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown here. Second, some subjects (n = 33 to 65) did not participate in the follow-up surveys of cognitive function performed in 1992, 1998, and 2005, and their cognitive conditions were evaluated only by mail or telephone. This might have resulted in failure to detect dementia cases. However, we also collected information on the development of dementia in another way, namely through the daily monitoring system established in the town. Thus, we believe that we detected almost all dementia cases, and this bias did not affect our findings. Third, the diagnosis of dementia was verified by autopsy only in 50.9% of dementia cases, resulting in a certain degree of subtype misclassification; agreement rate between clinical diagnosis and neuropathologic diagnosis was not high (64.4%) in our autopsy cases of dementia. However, a sensitivity analysis using only definite cases of dementia determined by brain autopsy did not make any material difference in our findings.

Our findings emphasize the need to consider diabetes as a potential risk factor for all-cause dementia, AD, and probably VaD. The other main finding, that elevated 2-hour PG levels are closely associated with increased risks of all-cause dementia and its subtypes, supports the view that postprandial glucose regulation is critical to prevent future dementia. Further investigations are required to clarify the associations between 2-hour PG levels by the OGTT and subtypes of dementia in other ethnic populations.

AUTHOR CONTRIBUTIONS

Tomoyuki Ohara contributed to the study concept, design, data collection, endpoint adjudication, interpretation of data, statistical analysis, and writing the manuscript. Yasufumi Doi contributed to the study concept, design, interpretation of data, statistical analysis, and writing the manuscript. Toshiharu Ninomiya contributed to the data collection, endpoint adjudication, interpretation of data, and statistical analysis. Yoichiro Hirakawa and Jun Hata contributed to data collection and interpretation of data. Toru Iwaki and Shigenobu Kanba contributed to endpoint adjudication and interpretation of data. Yutaka Kiyohara is a study coordinator and contributed to the study performance, obtaining supporting sources, study concept, design, endpoint adjudication, interpretation of data, and writing of manuscript. All authors critically reviewed the manuscript and approved final version.

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DISCLOSURE

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N-Terminal Pro-Brain Natriuretic Peptide and Risk of Cardiovascular Events in a Japanese Community

The Hisayama Study

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Objective—Few studies have examined the association between natriuretic peptides and the incidence of cardiovascular disease (CVD) in Asian populations.

Methods and Results—A total of 3104 community-dwelling Japanese individuals aged ≥40 years without history of CVD were followed up for 5 years. A total of 127 CVD events were identified. The age- and sex-adjusted incidence of CVD increased with increasing N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (<55, 55–124, 125–399, and ≥400 pg/mL) at baseline and was significantly higher even in subjects with a modest increase. This association remained robust even after adjustment for other potential risk factors (55–124 pg/mL: multivariate-adjusted hazard ratio=1.85 [95% CI 1.07–3.18], P=0.03; 125–399 pg/mL: 2.98 [95% CI 1.65–5.39], P<0.001; ≥400 pg/mL: 4.54 [95% CI 2.22–9.29], P<0.001). The multivariate-adjusted hazard ratios for the development of total CVD and its subtypes, coronary heart disease and stroke, were significantly increased by a 1 SD increment of the log NT-proBNP concentrations and were nearly equal among CVD subtypes. Similar findings were observed for stroke subtypes of ischemic stroke and intracerebral hemorrhage but not subarachnoid hemorrhage. The effects of the 1 SD increment in log NT-proBNP values were comparable in subjects with and without other cardiovascular risk factors, except for sex. The area under the receiver operating characteristic curve was significantly (P=0.006) increased by adding NT-proBNP values to the model including other potential risk factors.

Conclusion—Elevated NT-proBNP levels were shown to be a significant risk factor for the development of CVD and its subtypes in a general Japanese population, independently of other cardiovascular risk factors. (***Arterioscler Thromb Vasc Biol.* 2011;31:00-00.**)

Key Words: coronary artery disease ■ epidemiology ■ risk factors ■ stroke ■ cohort study

B-type natriuretic peptide (BNP) is a cardiac hormone secreted from the myocardium in response to increased ventricular stretch and wall tension. The precursor of BNP is split equimolarly into a biologically active peptide and a more stable N-terminal fragment (N-terminal pro-BNP [NT-proBNP]).[1,2] Measurement of circulating BNP or NT-proBNP levels has been recommended in the diagnosis and prognosis of patients with symptoms of left ventricular dysfunction[3] and for stratification of prognosis in patients with acute coronary syndromes.[4,5] Several prospective studies of community-dwelling persons have focused on the association between BNP/NT-proBNP and the risk of cardiovascular disease (CVD), particularly in white populations.[6–11] However, it is not certain to what extent these findings apply to general Asian populations. In addition, to the best of our knowledge, no studies have evaluated the association between BNP/NT-proBNP levels and hemorrhagic stroke, which has pathophysiological mechanisms different from those of thrombotic diseases.

The objective of the current study was to examine the associations between NT-proBNP levels at baseline and the development of CVD and its subtypes in a general Japanese population, taking into account comprehensive confounders.

Methods

Study Population

A population-based prospective study of CVD and its risk factors has been under way since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. The age, occupational distributions, and nutritional intake of the population were almost identical to those of the general Japanese population, based on data from the national census and nutrition survey.[12] In 2002, a baseline survey for the present study was performed in the town. A detailed description of this survey was published previously.[13] Briefly, of all residents aged ≥40 years, 3328 underwent

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examination (participation rate, 77.6%). A total of 224 individuals were subsequently excluded from the study; among these, 30 subjects did not consent to participate in the study, 190 had a history of CVD, and 4 had an insufficient quantity of stored sera for NT-proBNP measurement. Overall, 3104 individuals (1303 men and 1801 women) were enrolled in the study.

Follow-Up Survey

The subjects were followed up prospectively for 5 years, from 2002 to 2007, by repeated health examinations. The health status was checked yearly by mail or telephone for subjects who did not undergo a regular examination or who had moved away from town. We also established a daily monitoring system among the study team, local physicians, and members of the town's Health and Welfare Office. Using this system, we gathered information on new CVD events, including suspected cases. When coronary heart disease or stroke occurred or was suspected, physicians in the study team examined the subject and evaluated his or her detailed clinical information. The clinical diagnosis of coronary heart disease or stroke was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. Additionally, when a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, no subject was lost to follow-up, and 192 subjects died, of whom 129 (67.2%) underwent autopsy.

Definition of End Points

The outcomes of the present analysis were incidence and mortality of CVD. Total CVD was diagnosed as the development of coronary heart disease and stroke, and CVD death was defined as I00 to I99 of International Classification of Diseases-10.

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, and autopsy findings.[14] In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. Stroke was further divided into ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke.[15]

The criteria for the diagnosis of coronary heart disease included acute and silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diagnosis of myocardial infarction was based on detailed clinical information and at least 2 of the following findings: typical clinical symptoms; ECG evidence of myocardial infarction; elevated cardiac enzymes; and morphological findings, including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury, and autopsy findings. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes.

During the follow-up, 127 first-ever CVD events (77 men and 50 women) and 48 CVD deaths occurred. Among the CVD events, there were 49 cases of coronary heart disease (36 cases of myocardial infarction, 8 of coronary artery angioplasty, 2 of coronary artery bypass grafting, and 3 of sudden cardiac death) and 83 of stroke (54 cases of ischemic stroke, 19 of intracerebral hemorrhage, 9 of subarachnoid hemorrhage, and 1 of unclassified stroke).

Clinical Evaluation and Laboratory Measurement

At the screening examination, a portion of a serum specimen was stored at −80°C until it was used for the measurement of NT-proBNP concentrations in 2009. NT-proBNP levels were measured using a second-generation commercial kit, the Elecsys proBNP Immunoassay,[16] on an Elecsys 2010 platform.

Serum creatinine was measured by the enzymatic method using a fresh blood sample. The estimated glomerular filtration rate (eGFR) was calculated using the following modified equation of the Modification of Diet in Renal Disease Study for Japanese[17]:

$$\text{eGFR (mL/min per 1.73 m}^2) = 0.808 \times 175 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.741\ [\text{Japanese coefficient}]) \times (0.742 \text{ if female}).$$

Urine creatinine and albumin were measured using a spot urine sample by the turbidimetric immunoassay method. The urine albumin-creatinine ratio (mg/g) was calculated by dividing the urinary albumin values by the urinary creatinine concentrations. Chronic kidney disease was defined as an eGFR of <60 mL/min per 1.73 m^2 or a urine albumin-creatinine ratio of ≥30 mg/g according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines.[18] Plasma glucose concentrations were determined by the glucose-oxidase method. Diabetes was defined as fasting glucose concentrations ≥7.0 mmol/L), 2-hour postload or postprandial glucose concentrations ≥11.1 mmol/L, or taking antidiabetic medications. Total and high-density lipoprotein cholesterol levels were determined enzymatically, and hypercholesterolemia was defined as a total cholesterol level of ≥5.69 mmol/L.

Blood pressure was obtained 3 times using an automated sphygmomanometer (BP-203RV III, Colin, Tokyo, Japan) with the subject in a sitting position; the average of the 3 measurements was used in the present analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current treatment with antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 4-2, or 4-3), or atrial fibrillation (8-3).

Height and weight were measured with the subject wearing light clothes without shoes, and body mass index (BMI) (kg/m^2) was calculated. Obesity was defined as a BMI level of ≥25 kg/m^2. Each participant completed a self-administered questionnaire covering medical history, smoking habits, alcohol intake, and exercise. Smoking habits and alcohol intake were classified as either current habitual use or not. Those subjects who were engaged in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group.

Statistical Analysis

NT-proBNP levels were divided into 4 categories: <55, 55 to 124, 125 to 399, and ≥400 pg/mL according to the prior reports.[3,19,20] Age- and sex-adjusted mean values for possible risk factors were calculated by analysis of covariance, and their trends across NT-proBNP levels were tested by multiple regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. The incidence of CVD was calculated by the person-year method and was adjusted for age and sex by the direct method using 10-year age groupings. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and their 95% CIs were calculated using Cox proportional hazards model. The linear trends of HRs across NT-proBNP levels were also tested using the Cox proportional hazards model. Comparisons of the effects of increased NT-proBNP values between participants with and without other cardiovascular risk factors were made by adding an interaction term to the statistical model. To compare the accuracy of risk assessment for CVD development between the models adjusted for potential risk factors with and without NT-proBNP values, receiver operating characteristic (ROC) curves for the model were plotted. The consistency in the area under the ROC curve between the models was estimated using the method of DeLong et al.[21] All analyses were performed using the SAS software package version 9.2 (SAS Institute Inc, Cary, NC). Values of $P<0.05$ were considered statistically significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from all the participants.

Table 1. Age- and Sex-Adjusted Mean Values or Frequencies of Possible Risk Factors According to NT-proBNP Levels at Baseline, 2002

	NT-proBNP levels (pg/ml)				
Risk Factor*	<55 (n=1606)	55–124 (n=915)	125–399 (n=444)	≥400 (n=139)	*P* value
Age, y	55 (9)	64 (11)	73 (11)	78 (11)	<0.001
Men, %	49.6	32.7	32.2	46.0	<0.001
Systolic blood pressure, mm Hg	130 (22)	133 (20)	136 (22)	133 (21)	<0.001
Diastolic blood pressure, mm Hg	78 (13)	79 (12)	79 (13)	76 (12)	0.94
Hypertension, %	37.3	46.0	50.0	45.1	<0.001
ECG abnormalities, %	10.0	15.2	30.2	54.6	<0.001
Estimated GFR, mL/min per 1.73 m^2	84 (22)	85 (21)	82 (22)	72 (22)	<0.001
Chronic kidney disease, %	19.8	24.8	36.5	57.0	<0.001
Body mass index, kg/m^2	23.5 (3.6)	23.0 (3.4)	22.3 (3.6)	21.5 (3.5)	<0.001
Obesity, %	29.4	24.7	19.3	19.3	<0.001
Diabetes mellitus, %	16.9	16.0	21.4	17.6	0.58
Total cholesterol, mmol/L	5.45 (0.97)	5.17 (0.90)	5.04 (0.96)	4.81 (0.94)	<0.001
Hypercholesterolemia, %	35.3	25.3	23.5	10.6	<0.001
HDL cholesterol, mmol/L	1.60 (0.44)	1.64 (0.41)	1.64 (0.44)	1.64 (0.42)	0.10
Current drinking, %	44.1	43.2	43.0	31.8	0.95
Current smoking, %	21.0	24.2	23.1	21.8	0.32
Regular exercise, %	10.6	10.1	6.9	4.8	0.01

The mean age and frequency of men were not adjusted. All values are given as means (SD) or as percentages. NT-proBNP indicates N-terminal pro-brain natriuretic peptide; GFR, glomerular filtration rate; HDL, high-density lipoprotein.

*Hypertension: blood pressures of ≥140/90 mm Hg or current use of antihypertensive medicine. Chronic kidney disease: estimated glomerular filtration rate <60 mL/min per 1.73m^2 or a urine albumin-creatinine ratio of ≥30 mg/g. Obesity: body mass index ≥25 kg/m^2. Hypercholesterolemia: total cholesterol ≥5.69 mmol/L. Diabetes mellitus: fasting ≥7.0 mmol/L, 2-h postload or postprandial glucose levels ≥11.1 mmol/L, or use of hypoglycemic agents. ECG abnormalities: left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 4-2, or 4-3), or atrial fibrillation (8-3).

Results

The baseline characteristics of the study population according to the 4 categories of NT-proBNP values are summarized in Table 1. The mean values of age and systolic blood pressure and the frequencies of hypertension, ECG abnormalities, and chronic kidney disease increased with increasing NT-proBNP levels, whereas the mean values of eGFR, BMI, and total cholesterol and the frequencies of men, obesity, hypercholesterolemia, and regular exercise declined significantly with rising NT-proBNP levels.

Table 2 shows the age- and sex-adjusted incidence of CVD according to NT-proBNP levels. A significant association was observed between NT-proBNP levels and the incidence of total CVD. In regard to subtypes of CVD, the incidence of coronary heart disease and stroke increased significantly as the NT-proBNP levels increased. Similar findings were observed in stroke subtypes of ischemic stroke and intracerebral hemorrhage, but not subarachnoid hemorrhage. The HR for the development of total CVD increased with increasing NT-proBNP levels and was significantly higher even in subjects with NT-proBNP levels of 55 to 124 pg/mL compared with those with NT-proBNP levels of <55 pg/mL after adjustment for age, sex, systolic blood pressure, ECG abnormalities, eGFR, BMI, diabetes, total and high-density lipoprotein cholesterol levels, smoking habits, alcohol intake, and regular exercise. Furthermore, when estimating the age- and sex-adjusted and multivariate-adjusted HRs for a 1 SD increment in log-transformed NT-proBNP concentrations, we found significant upward trends for the development of total CVD and its subtypes (ie, coronary heart disease and stroke, including ischemic stroke and intracerebral hemorrhage), and the magnitude of the influence of the 1 SD increment in log NT-proBNP concentrations was almost equal among CVD subtypes (Table 2).

In the same way as the CVD incidence, the age- and sex-adjusted mortality from CVD increased with increasing NT-proBNP levels and was significantly higher in subjects with NT-proBNP levels of 125 to 399 pg/mL compared with those with the lowest NT-proBNP levels (Table 2). This association remained unchanged even after adjustment for the confounding factors mentioned above.

The age- and sex-adjusted HRs for the development of total CVD owing to a 1 SD increment in log NT-proBNP concentrations, in subjects with and without other cardiovascular risk factors, are shown in Figure 1. Comparable effects of a 1 SD increment in log NT-proBNP concentrations on the risk of total CVD were observed in subjects aged 40 to 64 years and those aged ≥65 years (*P* for heterogeneity=0.82). A sex difference in the influence of a 1 SD increment in log NT-proBNP concentrations on the incidence of CVD was identified, although the association between log NT-proBNP concentrations and the incidence of CVD was statically

Table 2. Adjusted Incidences, Mortalities, and Hazard Ratios of Cardiovascular Disease and Its Subtypes According to NT-proBNP Levels, 2002 to 2007

	NT-proBNP levels (pg/ml)				*P* for Trend (Across Categories)	Continuous Log Scale*	*P* for Trend (Continuous)
	<55 (n=1606)	55–124 (n=915)	125–399 (n=444)	≥400 (n=139)			
Total cardiovascular disease incidence							
No. of events/person-y	25/8304	37/4641	41/2082	24/542			
Age and sex incidence†	4.0	8.6	14.2	38.6			
Age- and sex-adjusted HR (95% CI)	1 (reference)	1.89 (1.10–3.24)	3.26 (1.83–5.80)	4.99 (2.55–9.74)	<0.001	1.71 (1.45–2.02)	<0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	1.85 (1.07–3.18)	2.98 (1.65–5.39)	4.54 (2.22–9.29)	<0.001	1.85 (1.51–2.27)	<0.001
Coronary heart disease							
No. of events/person-y	9/8339	16/4691	15/2150	9/574			
Age and sex incidence†	1.8	3.6	4.0	6.0			
Age- and sex-adjusted HR (95% CI)	1 (reference)	2.11 (0.88–5.05)	2.98 (1.16–7.67)	4.18 (1.41–12.42)	0.007	1.63 (1.25–2.13)	<0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	2.21 (0.92–5.30)	3.04 (1.15–8.04)	4.46 (1.38–14.39)	0.01	1.85 (1.33–2.57)	<0.001
Total stroke							
No. of events/person-y	16/8318	22/4656	30/2095	15/552			
Age and sex incidence†	2.2	5.2	10.9	31.9			
Age- and sex-adjusted HR (95% CI)	1 (reference)	1.77 (0.90–3.50)	3.81 (1.88–7.74)	5.20 (2.24–12.06)	<0.001	1.75 (1.43–2.14)	<0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	1.62 (0.82–3.21)	3.09 (1.49–6.41)	4.03 (1.65–9.87)	<0.001	1.79 (1.40–2.30)	<0.001
Ischemic stroke							
No. of events/person-y	8/8318	15/4656	20/2095	11/552			
Age and sex incidence†	1.2	3.6	6.8	29.0			
Age- and sex-adjusted HR (95% CI)	1 (reference)	2.26 (0.92–5.55)	4.54 (1.77–11.59)	6.61 (2.25–19.42)	<0.001	1.78 (1.39–2.28)	<0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	2.15 (0.87–5.35)	4.24 (1.62–11.09)	6.41 (2.04–20.20)	<0.001	1.97 (1.45–2.69)	<0.001
Intracerebral hemorrhage							
No. of events/person-y	4/8318	5/4656	7/2095	3/552			
Age and sex incidence†	0.6	1.1	3.3	2.1			
Age- and sex-adjusted HR (95% CI)	1 (reference)	2.16 (0.54–8.64)	5.71 (1.36–24.00)	7.04 (1.21–40.88)	0.009	1.87 (1.29–2.72)	0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	1.82 (0.45–7.37)	3.81 (0.88–16.50)	4.09 (0.64–26.07)	0.07	1.84 (1.12–3.02)	0.02
Subarachnoid hemorrhage							
No. of events/person-y	4/8318	2/4656	2/2095	1/552			
Age and sex incidence†	0.4	0.5	0.6	0.8			
Age- and sex-adjusted HR (95% CI)	1 (reference)	0.55 (0.09–3.36)	0.81 (0.11–6.19)	1.29 (0.10–17.53)	0.97	1.20 (0.54–2.65)	0.65
Multivariable-adjusted HR (95% CI)	1 (reference)	0.42 (0.07–2.60)	0.33 (0.04–2.94)	0.41 (0.02–6.77)	0.39	0.79 (0.31–2.00)	0.63
Cardiovascular disease mortality							
No. of events/person-y	2/8353	12/4709	16/2163	18/584			
Age and sex mortality†	0.5	2.4	6.2	12.3			
Age- and sex-adjusted HR (95% CI)	1 (reference)	3.91 (0.85–18.02)	5.25 (1.11–24.83)	12.70 (2.57–62.72)	<0.001	1.93 (1.46–2.56)	<0.001
Multivariable-adjusted HR (95% CI)	1 (reference)	4.08 (0.88–18.89)	5.60 (1.15–27.27)	12.87 (2.44–67.75)	<0.001	2.22 (1.57–3.14)	<0.001

Multivariable adjustment was made for age, sex, systolic blood pressure, electrocardiogram abnormalities, estimated glomerular filtration rate, body mass index, diabetes, total and high density lipoprotein cholesterol levels, smoking habits, alcohol intake, and regular exercise. The adjusted HR included the interaction term of sex and NT-proBNP in the model. NT-proBNP indicates N-terminal pro-brain natriuretic peptide; HR, hazard ratio.

*HR per 1 SD increase of log NT-proBNP.

†Per 1000 person-y.

significant in both sexes. There were no clear differences in the effects of NT-proBNP in subjects with and without other cardiovascular risk factors, such as hypertension, chronic kidney disease, obesity, diabetes, hypercholesterolemia, and smoking (all probability values for heterogeneity >0.05).

To evaluate the influence of NT-proBNP levels on the accuracy of CVD risk assessment, we compared the area under the ROC curve between models with and without NT-proBNP values (Figure 2). The area under the ROC curve was significantly increased by adding NT-proBNP values to the model including the potential risk factors mentioned above (from 0.820 to 0.841; *P* for difference in the area=0.006). The same was true for the respective CVD subtypes—ie, coronary heart disease and stroke (data not shown).

To compare the ability of NT-proBNP to predict future CVD with other risk factors, we estimated the areas under the ROC curves, adding continuous values of risk factors to the age- and sex-adjusted model. As a result, the area under the ROC curve was significantly larger for NT-proBNP (0.816) than for other risk factors, namely, systolic blood pressure (0.795),

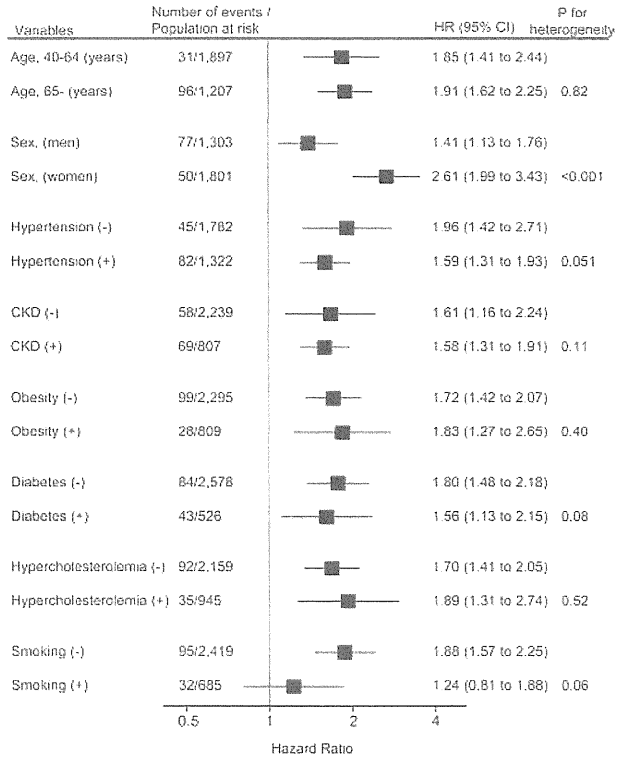
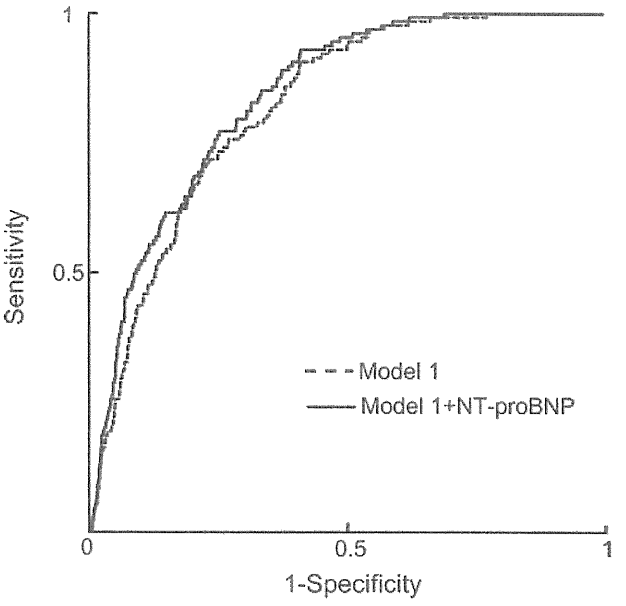


Figure 1. Age- and sex-adjusted hazard ratios for the development of cardiovascular disease owing to a 1 SD increment in log NT-proBNP concentrations by the presence or absence of other cardiovascular risk factors. CKD indicates chronic kidney disease; NT-proBNP, N-terminal pro-brain natriuretic peptide.



Model	Area under curve (95% CI)	P value (vs. Model 1)
Model 1	0.820 (0.790 to 0.851)	-
Model 1+NT-proBNP	0.841 (0.812 to 0.870)	0.006

Figure 2. Comparison of the accuracy of risk assessment for the development of cardiovascular disease. Model 1 includes age, sex, systolic blood pressure, ECG abnormalities, estimated glomerular filtration rate, body mass index, diabetes, total and high-density lipoprotein cholesterol levels, smoking habits, alcohol intake, and regular exercise. The area under the receiver operating characteristic curve was compared between model 1 alone and model 1 including NT-proBNP values. NT-proBNP indicates N-terminal pro-brain natriuretic peptide.

eGFR (0.784), BMI (0.782), total cholesterol (0.786), and high-density lipoprotein cholesterol (0.783) (all $P<0.05$).

Discussion

In a prospective study of a general Japanese population, we clearly demonstrated that the risk for the development of CVD and its subtypes increased with increasing NT-proBNP levels and was significantly higher even in subjects with a modest increase in NT-proBNP. This association remained robust even after controlling for other confounding factors. The magnitude of the influence of NT-proBNP was nearly equal among CVD subtypes and larger than other risk factors. These findings suggest that high NT-proBNP levels are an independent and strong risk factor for the development of various types of CVD.

Several cohort studies have indicated that elevated BNP/NT-proBNP levels increased the risk of total CVD,[6–11] coronary heart disease,[6,8,11] and stroke.[6,7,9,11] However, very few prospective studies have provided evidence of associations between the natriuretic peptide levels and CVD in Asian populations.[9,22] One cohort study of a Japanese population showed an association between increased BNP levels and the risk of developing ischemic stroke.[9] Another clinical observational study in Japan also revealed a significant influence of elevated BNP levels on CVD events, but this association was not observed for coronary heart disease.[22] The present study confirmed the results from the prior studies and provided more detailed information regarding the risks of various CVDs, including coronary heart disease and stroke. To the best of our knowledge, this is the first report to show that elevated NT-proBNP levels are an independent risk factor for the occurrence of intracerebral hemorrhage. In addition, in our study, a 1 SD increase in log NT-proBNP values was linked to an 85% increase in the total risk of CVD after adjustment for other traditional risk factors, and the magnitude of the influence of elevated log NT-proBNP concentrations was almost equal among CVD subtypes: namely, coronary heart disease, ischemic stroke, and intracerebral hemorrhage. In white population–based studies, a 1 SD increase in log NT-proBNP concentrations was associated with a 35% to 92% increase in the risk of major CVD events.[6,7,11] These findings imply that the measurement of NT-proBNP values is valuable for identifying individuals at high risk of CVD independent of ethnicity.

In our study, NT-proBNP levels were inversely related to obesity and hypercholesterolemia and positively related to age and blood pressure levels and the prevalence of chronic kidney disease. Nevertheless, the inclusion of these factors in the model did not attenuate the overall association between NT-proBNP levels and total CVD, and adding NT-proBNP values to potential risk factors significantly increased the area under the ROC curve. Furthermore, our study revealed no

interactions between the various risk factors and NT-proBNP values, with the exception of sex. These findings imply that NT-proBNP is a novel and universal risk factor for various types of CVD and may improve the risk prediction of future CVD events in general populations beyond the estimation afforded by classical risk factors.

The mechanisms underlying the association between natriuretic peptides and the risks of CVDs are still unknown. A cross-sectional study found that high NT-proBNP levels were independently associated with higher coronary artery calcium scores as evaluated by electron beam computed tomography in subjects without heart failure or renal dysfunction.[23] This fact raises the possibility that BNP/NT-proBNP levels are correlated with the degree of systemic atherosclerosis. Because elevated natriuretic peptides reflect increased ventricular stretch from volume as well as pressure overloads,[2] subjects with these overloads might have vascular stretch and wall tension, which could contribute to the development of CVD. However, NT-proBNP levels are considered a surrogate marker because medication with BNP has an effect on relaxation, but not on tension, of the human arteries.[24 25] To date, no specific pathological role of natriuretic peptides has been identified in inflammation, oxidative stress, or abnormalities in coagulation and fibrinolytic pathways, which are considered to be the major pathological mechanisms involved in the atherosclerotic process. Additional studies are needed to reveal the mechanisms of the association between NT-proBNP levels and vascular damage.

The strengths of our study include its longitudinal population-based design, low selection bias, perfect follow-up of subjects, and accuracy of diagnosis of CVD subtypes. One limitation of our study is that the evaluation of NT-proBNP values was based on a single measurement at baseline, as is the case in most epidemiological studies. During the follow-up, the levels were changed because of modifications in lifestyle or medication, and misclassification of NT-proBNP levels was possible. This could have weakened the association found in this study, biasing the results toward the null hypothesis. Therefore, the true association may be stronger than that shown in our study.

In conclusion, the present analysis clearly showed that elevated NT-proBNP levels were a novel risk factor for CVD and its subtypes—ie, coronary heart disease and stroke— in a general population of Japanese. This study also demonstrated the potential applicability of NT-proBNP measurement to epidemiological studies; such an approach may be suitable for large-scale screening programs to evaluate the risk of CVD, including coronary heart disease and stroke.

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Disclosures

None.

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Association of Alzheimer disease pathology with abnormal lipid metabolism

The Hisayama Study

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ABSTRACT

Objective: The relationship between lipid profiles and Alzheimer disease (AD) pathology at the population level is unclear. We searched for evidence of AD-related pathologic risk of abnormal lipid metabolism.

Methods: This study included brain specimens from a series of 147 autopsies performed between 1998 and 2003 of residents in Hisayama town, Japan (76 men and 71 women), who underwent clinical examinations in 1988. Lipid profiles, such as total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDLC), were measured in 1988. Low-density lipoprotein cholesterol (LDLC) was calculated using the Friedewald formula. Neuritic plaques (NPs) were assessed according to the Consortium to Establish a Registry for Alzheimer's Disease guidelines (CERAD) and neurofibrillary tangles (NFTs) were assessed according to Braak stage. Associations between each lipid profile and AD pathology were examined by analysis of covariance and logistic regression analyses.

Results: Adjusted means of TC, LDLC, TC/HDLC, LDLC/HDLC, and non-HDLC (defined as TC-HDLC) were significantly higher in subjects with NPs, even in sparse to moderate stages (CERAD = 1 or 2), compared to subjects without NPs in multivariate models including *APOE* ε4 carrier and other confounding factors. The subjects in the highest quartiles of these lipid profiles had significantly higher risks of NPs compared to subjects in the lower respective quartiles, which may suggest a threshold effect. Conversely, there was no relationship between any lipid profile and NFTs.

Conclusion: The results of this study suggest that dyslipidemia increases the risk of plaque-type pathology. *Neurology*® 2011;77:1068-1075

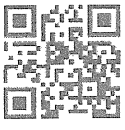
GLOSSARY

AD = Alzheimer disease; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **HDLC** = high-density lipoprotein cholesterol; **LDLC** = low-density lipoprotein cholesterol; **NFT** = neurofibrillary tangle; **NP** = neuritic plaque; **OR** = odds ratio; **TC** = total cholesterol; **TG** = triglycerides.

To elucidate the association of lifestyle diseases with Alzheimer disease (AD) pathology, a large-scale, population-based clinicopathologic study is required. Since 1961, we have been conducting a long-term prospective cohort study of cerebro-cardiovascular diseases in the town of Hisayama, a suburb of Fukuoka City in Japan. Careful surveillance of cognitive impairment was started from 1985, which was carried out through a daily monitoring system established by the study team, local practitioners, and the town government. In a series of studies, we have reported the incidence and survival of dementia,[1] and trends in the prevalence of AD and vascular dementia.[2] These studies indicate that the prevalence of AD is increasing at an accelerating pace in parallel with an increase of metabolic disorders. Recently, we also reported that insulin

Supplemental data at www.neurology.org

Supplemental Data



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