ABSTRACT

Objective: To estimate the incidence and survival rates of total and cause-specific dementia in a general Japanese population.

Methods: A total of 828 subjects without dementia, aged 65 years or over, were followed up prospectively for 17 years. Dementia was subdivided into cause-specific subtypes: namely, Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), combined dementia, and other types of dementia. During the follow-up, 275 subjects developed dementia; of these, 251 (91.2%) were evaluated morphologically, with 164 subjected to brain autopsy examination and the remaining 87 to neuroimaging.

Results: The incidences of total dementia, AD, VD, DLB, combined dementia, and other types of dementia were 32.3 (n=275), 14.6 (124), 9.5 (81), 1.4 (12), 3.8 (33), and 3.1 (16) per 1,000 person-years, respectively. The incidences of AD, combined dementia, and other types of dementia rose with increasing age, particularly after the age of 85 years, but this tendency was not observed for VD or DLB. The survival curve of dementia cases aged 65 to 89 years was significantly lower than that of age- and sex-matched controls (10-year survival rate, 13.6% vs. 29.3%; hazard ratio, 1.67; 95% confidence interval, 1.31-2.13). The 10-year survival rates were not significantly different among dementia subtypes.

Conclusions: Our findings suggest that the Japanese elderly population has a high risk of the development of dementia, specifically AD and VD, and once dementia is established, the risk of death is considerable.

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 elderly worldwide.[1] Effective prevention requires a strategy based on information about morbidity and mortality from dementia in general populations. Several population-based studies have investigated the incidence[2-9] and fatality rates[10-13] of total and cause-specific dementia, but the current knowledge about the incidence and prognosis of dementia was derived mainly from studies done in Western populations, and it is unclear to what extent these findings apply to Japanese elderly populations. Here we present the incidence and survival of cause-specific dementia in a 17-year follow-up study conducted in a Japanese community.

METHODS

Study population

Since 1985, a follow-up survey of dementia among individuals aged 65 years or older has been ongoing in the town of Hisayama, Japan.[9] The screening and assessment processes of the present analysis are shown in figure 1. In 1985, a total of 887 subjects aged 65 years or older (participation rate, 94.6%) underwent a screening examination that included Hasegawa's dementia scale (HDS),[14] which is a neuropsychological test widely utilized in Japan comprised of 11 questions regarding orientation, memory function, common knowledge, and calculation capacities, and questionnaires regarding psychological and medical symptoms, medical conditions, and activities of daily living. The subjects with possible cognitive impairment underwent comprehensive investigations. After excluding 59 subjects with dementia at baseline, the remaining 828 subjects were enrolled in this study.

Follow-up survey

The subjects were followed prospectively from November 1985 to October 2002 (figure 1). Detailed information about the follow-up survey of dementia has been described elsewhere.[9] Briefly, we established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. Regular health checks were given annually to obtain information on any stroke or dementia missed by the monitoring network. Health status was also checked yearly by mail or telephone for any subject who did not undergo a regular examination or who had moved out of town.

Follow-up screening surveys of cognitive function were conducted in 1992,[15] 1998, and 2005. The screening surveys included neuropsychological tests (HDS,[14] HDS revised version [HDS-R],[16] or Mini-Mental State Examination [MMSE][17]) and questionnaires similar to those employed at the first screening. For subjects whose test scores were below the cut-off points (22/32.5 for HDS, 21/30 for the 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.

When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 553 subjects died, 439 of whom (79.4%) were subjected to autopsy. For dementia subjects with autopsy, detailed neuropathological evaluation was performed. No subject was lost in the follow-up.

Diagnosis of dementia

The diagnosis of dementia was made clinically based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R).[18]

Alzheimer's disease (AD), vascular dementia (VD), and dementia with Lewy bodies (DLB) were diagnosed based on the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[19] the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),[20] and the revised consensus guidelines described in the third report of the DLB consortium,[21] respectively.

For neuropathological evaluation of AD, the frequency of senile plaques and neurofibrillary tangles (NFT) was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria[22] and Braak stage.[23] The CERAD score and Braak stage were combined using the National Institute on Aging-Reagan Institute (NIA-RI) criteria,[24] and dementia cases with 'high-likelihood' of AD pathology were defined as definite AD. Definite VD was defined as dementia with causative stroke or cerebrovascular change in neuroimaging and no neuropathological evidence of other forms of dementia. According to the DLB guidelines,[21] dementia cases with 'high-likelihood' criterion of DLB pathology were defined as definite DLB. Senile dementia of the neurofibrillary tangle type (tangle-only dementia: SD-NFT) was diagnosed neuropathologically using Yamada's guideline.[25,26]

During the 17-year follow-up period, 275 subjects developed dementia. Of these, 175 cases died, and 134 (76.6%) of these cases were subjected to brain autopsy examination (figure 1). The brains were evaluated neuropathologically in an additional 30 subjects with dementia who died after the end of the follow-up period, from November 2002 to October 2005. A total of 164 of the 275 subjects with dementia (59.6%) were examined neuropathologically. We performed evaluation with neuroimaging on 248 subjects with dementia (90.2%); among the 111 subjects with dementia who did not have an autopsy examination, 87 underwent neuroimaging examination. Therefore, 251 subjects with dementia (91.2%) were evaluated morphologically.

In the present analysis, we used the final diagnosis of dementia subtypes, which was made based on the clinical and neuropathological information for dementia subjects with autopsy and clinical information including neuroimaging only for those without autopsy. Table 1 shows a comparison of the clinical diagnosis of dementia subtype, which was made without information on neuropathological findings, and the final diagnosis, which was made using neuropathological findings, among 164 incident dementia cases with autopsy. Though the clinical diagnosis was not necessarily same as the final diagnosis, moderate agreement was observed between the clinical and final diagnoses (agreement rate=60%, kappa coefficient=0.48 for AD; agreement rate=59%, kappa coefficient=0.53 for VD). Table 2 shows the frequency of each type of dementia among 275 incident dementia cases. We found 124 pure AD cases (definite, 62; probable, 52; possible, 10), 81 pure VD cases (definite, 50; probable, 31), and 12 pure DLB cases (definite, 9; probable, 2; possible, 1). When causes of cognitive impairment were attributed to two or more types of dementia, we classified the dementia as "combined dementia." This category accounted for 33 cases. There were 16 cases of other types of dementia.

The date of onset of VD was determined as the date when the responsible stroke

occurred, but the final diagnosis of VD was made more than 3 months after the stroke. The tentative time of onset, when the family or attending physician first noticed abnormal behaviour by the subject, was used for other types of dementia.

Statistical analysis

The incidence of dementia was estimated using a person-year approach. We estimated survival curves for the first 10 years after the onset of dementia for 221 new-onset dementia cases with ages at dementia onset ranging from 65 to 89 years, and for 221 age- and sex-matched control subjects randomly selected from 553 subjects without incident dementia by the Kaplan-Meier product limit technique. We excluded subjects aged 90 years or over for this analysis, because the number of control subjects of this age group was too small. The comparison of survival rates was done by log-rank test. We also compared age- and sex-adjusted cumulative survival rates among cases with different types of dementia using Cox's proportional hazards model.

RESULTS

The incidence of total dementia was 32.3 per 1,000 person-years. In regard to type, AD was the most frequent type of dementia (14.6 per 1,000 person-years), VD second (9.5), and DLB third (1.4). The incidences of AD, combined dementia, and other types of dementia rose with increasing age, particularly after the age of 85 years, but this tendency was not observed for VD or DLB (figure 2).

Figure 3 shows the 10-year survival curves for new-onset dementia cases and control subjects without dementia onset. The survival curve of dementia cases was significantly lower compared to that of the control subjects (10-year survival rate, 13.6% vs. 29.2%; hazard ratio, 1.67; 95% confidence interval, 1.31-2.13; $P<0.0001$). The median survival time was 3.5 years in subjects with dementia and 5.8 years in those without dementia.

The age- and sex-adjusted survival curves for cases with different types of dementia are shown in figure 4. The survival rate of subjects with DLB tended to be lower than that of subjects with other types of dementia, but the differences were not significant, probably due to the small number of subjects with DLB (10-year survival rates, 18.9% for AD, 13.2% for VD, 2.2% for DLB, 10.4% for combined dementia, 14.4% for other types of dementia).

DISCUSSION

The present analysis from a prospective cohort study has clearly demonstrated that the incidence of dementia was as high as 32.3 per 1,000 person-years in a general population of Japanese elderly aged 65 years or older. We diagnosed dementia subtypes based on clinical and neuropathological examinations and found that AD, VD, and DLB were the three major subtypes of dementia in this population. Another important finding was that the median survival time of subjects with new-onset dementia was shorter than that of those without dementia onset.

Several population-based cohort studies have reported the incidence of dementia for elderly poplations[2-9]. The incidence of dementia of our study (32.3 per 1,000 person-years) was relatively higher than that obtained from the majority of other follow-up studies (13.5 to 25.5),[2-6] and similar to that of an Italian study (37.8)[7] and an African American study (32.4).[8] Possible reasons for the relatively higher incidence of

dementia in our study were the frequently repeated screening surveys for dementia and the high follow-up rate.

In our subjects, DLB was the third most-frequent type of dementia after AD and VD, with an incidence of 1.4 per 1,000 person-years. Although there have been several prevalence studies of DLB in general populations, little is known about the exact incidence of DLB.[27] Miech et al. estimated the incidence of DLB as 0.57 per 1,000 person-years in a U.S. population.[2] In contrast, no case of DLB was observed in the 4-year follow-up study of an Italian population.[7] It is possible that the higher incidence of DLB in our study resulted from a higher rate of neuropathological evaluation among subjects with dementia. Further cohort studies are needed to investigate the precise incidences of DLB.

In the present analysis, all types of dementia were associated with higher mortality, and the estimate of median survival time for subjects with total dementia was 3.5 years. This is shorter than that obtained from other population-based cohort studies (5.2 to 7.6 years).[10-13] Most previous cohort studies estimated median survival time in follow-up surveys of subjects having dementia at baseline examination. Therefore, it is possible that severe dementia cases with poor prognosis may not have been included, and that the survival time of patients with dementia may have been overestimated ("length bias"). In the Canadian Study of Health Aging, the crude median survival time was 6.6 years, but the estimated survival time from the onset of dementia after controlling for "length bias" was 3.3 years.[13] This finding is comparable to the median survival time from the onset of dementia observed in the present analysis.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, sufficient number of dementia events, 100% follow-up of subjects, and examination of the brains of most dementia cases with autopsy and neuroimaging. A limitation of our study is that relatively low cut-off points of neuropsychological tests for comprehensive investigations of dementia in the follow-up examinations may have caused us to miss subjects in the early course of dementia. This limitation may have led to an underestimation of the incidence of dementia and survival time. Another limitation is that we compared the survival rates among subjects matched by age at dementia onset ranging only within 65 to 89 years because the number of control subjects aged 90 years or older without dementia was too small. However, subjects aged 90 or older are not likely to live long, irrespective of the existence of dementia, and inclusion of subjects of this age group is not likely to have changed the findings of this study.

In conclusion, relatively more Japanese elderly suffer from dementia than the proportion expected based on the results of other follow-up studies. Once dementia is established, the risk of death is 1.7-fold higher compared to subjects without dementia. It is important to elucidate risk factors for each type of dementia and establish dementia prevention strategies, especially in countries such as Japan where the elderly population is increasing rapidly, as dementia places a burden on families and communities.

Competing interests
None.

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Ethics approval
The Ethics Committee of Kyushu University approved this study, and participants provided written informed consent for study participation.

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Figure Legends

Figure 1 Flow chart for screening and diagnostic procedures

Figure 2 Incidence rates of cause-specific dementia by age group

Figure 3 Survival rates and 95% confidence intervals for new-onset dementia cases and for age- and sex-matched control participants without dementia onset

Figure 4 Age- and sex-adjusted survival rates of cause-specific dementia

Table 1 Comparison of the clinical diagnosis of dementia subtype and the final diagnosis using neuropathological findings among 164 incident dementia cases with autopsy: the Hisayama Study, 1985-2002

Final diagnosis using neuropathological findings	Clinical diagnosis		
	AD (n=71)	VD (n=47)	Other (n=46)
Pure AD	35	16	11
Pure VD	17	21	12
DLB	2	1	6
Combined dementia	12	7	10
AD+VD	6	3	4
AD+DLB	3	2	1
VD+DLB	2	1	1
AD+VD+DLB	0	0	2
AD+chronic subdural hematoma	0	1	0
DLB+SD-NFT	0	0	1
AD+VD+hypothyroid	1	0	0
SD-NFT+carbon monoxide poisoning	0	0	1
Others	5	2	7

AD: Alzheimer's disease
VD: Vascular dementia
DLB: Dementia with Lewy bodies
SD-NFT: Senile dementia of the neurofibrillary tangle type

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Table 2 Frequency of each type of dementia among 275 incident dementia cases: the Hisayama Study, 1985-2002

Type of dementia	n (%)
Alzheimer's disease (AD)	124 (45.1)
Vascular dementia (VD)	81 (29.5)
Dementia with Lewy bodies (DLB)	12 (4.4)
Combined dementia	33 (11.6)
AD+VD	13 (4.7)
AD+DLB	9 (3.3)
VD+DLB	5 (1.8)
AD+VD+DLB	2 (0.7)
AD+chronic subdural hematoma	1 (0.4)
DLB+SD-NFT	1 (0.4)
AD+VD+hypothyroid	1 (0.4)
SD-NFT+carbon monoxide poisoning	1 (0.4)
Others	16 (6.2)
SD-NFT	8 (2.9)
Chronic subdural hematoma	2 (0.7)
Brain tumor	2 (0.7)
Head trauma	2 (0.7)
Pick's disease	1 (0.4)
Hypoxic ischemic encephalopathy	1 (0.4)
Unknown	9 (3.3)

SD-NFT: Senile dementia of the neurofibrillary tangle type

Figure 1

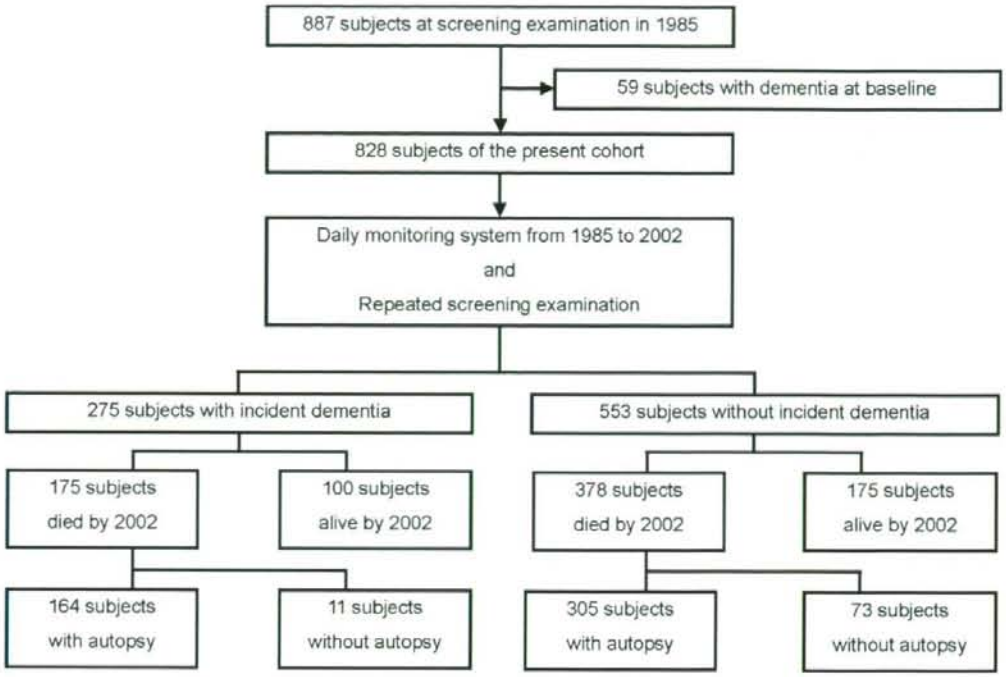


Figure 2

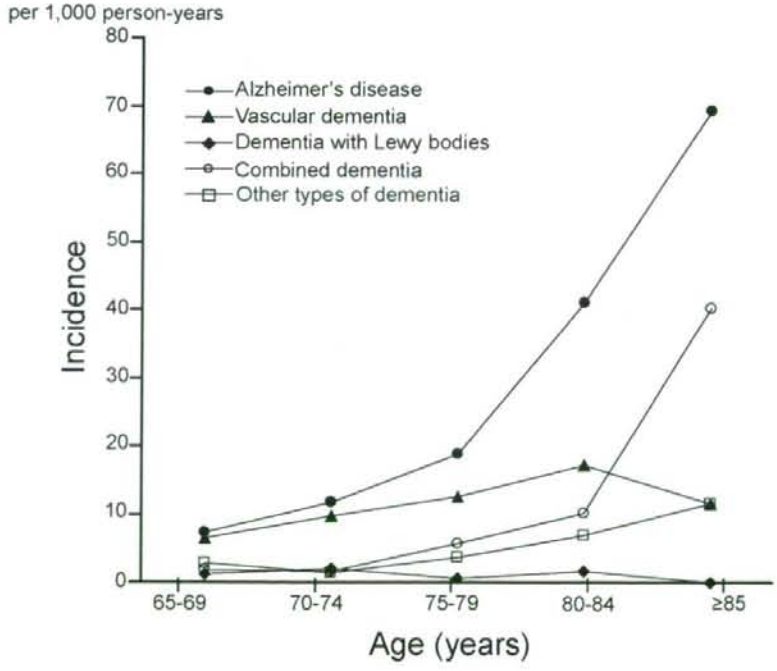


Figure 3

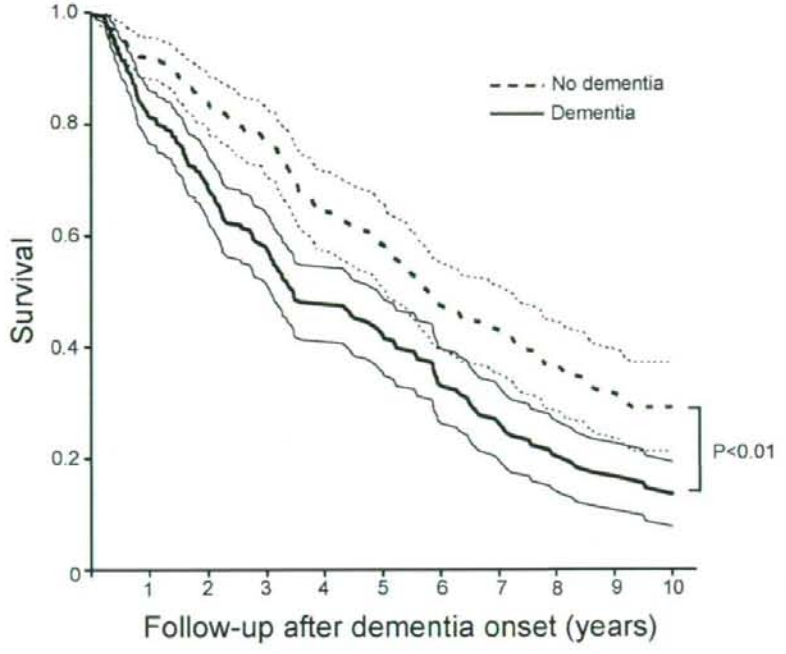
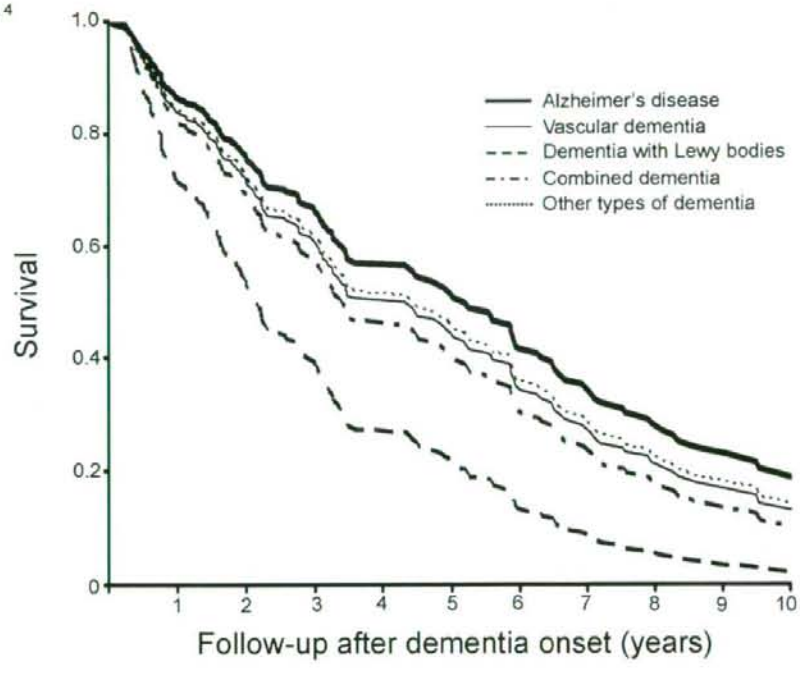


Figure. 4



High-Sensitivity C-Reactive Protein and Coronary Heart Disease in a General Population of Japanese

The Hisayama Study

Hisatomi Arima, Michiaki Kubo, Koji Yonemoto, Yasufumi Doi, Toshiharu Ninomiya, Yumihiro Tanizaki, Jun Hata, Kiyoshi Matsumura, Mitsuo Iida, Yutaka Kiyohara

Objective—The purpose of this study was to investigate the effects of high-sensitivity C-reactive protein (hs-CRP) on the risks of coronary heart disease (CHD) in a general population of Japanese.

Methods and Results—The Hisayama study is a population-based prospective cohort study. A total of 2589 participants aged 40 years or older were followed up for 14 years. Outcomes are incident CHD (myocardial infarction, coronary revascularization, and sudden cardiac death). The median hs-CRP level was 0.43 mg/L at baseline. During the follow-up period, 129 coronary events were observed. Age- and sex-adjusted annual incidence rates of CHD rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years for quartile groups defined by hs-CRP levels of <0.21, 0.21 to 0.43, 0.44 to 1.02, and >1.02 mg/L, respectively ($P<0.0001$ for trend). The risk of CHD in the highest quartile group was 2.98-fold (95% CI, 1.53 to 5.82) higher than that in the lowest group even after controlling for other cardiovascular risk factors.

Conclusions—hs-CRP levels were clearly associated with future CHD events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. (***Arterioscler Thromb Vasc Biol.* 2008;28:1385-1391**)

Key Words: inflammation ■ C-reactive protein ■ coronary heart disease ■ prospective cohort study ■ general population

Coronary heart disease (CHD) is estimated to be one of the leading causes of death in Japan as well as other countries around the world, placing a burden on the community.[1] Although the burden of CHD has been reduced in several developed countries in the past few decades,[2] its incidence rates have not declined in Japan.[3] Effective prevention will require a strategy based on knowledge of the importance of novel and traditional risk factors for CHD in Japan.

See accompanying article on page 1222

Recently, inflammation has emerged as an important factor in atherosclerosis,[4] and high-sensitivity C-reactive protein (hs-CRP) has attracted clinical attention as a novel risk factor for CHD. However, current knowledge of the importance of hs-CRP as a risk factor for CHD is derived mainly from studies done in Western populations,[5–12] and it is unclear to what extent these findings apply to Japanese populations. The Hisayama Study is a prospective cohort study of a general Japanese population. A previous report from the Hisayama Study showed a positive association between hs-CRP levels and the risks of ischemic stroke among Japanese men.[13] The objective of the present analysis is to examine the relationship between serum hs-CRP levels and future development of coronary heat disease in a general population of Japanese.

Methods

Study Design and Participants

Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[3,14] In 1988, a screening survey for the present study was performed in the town. A total of 2736 residents aged 40 years or older (80.9% of the total population of this age group) consented to participate in the examination.[13,15] After the exclusion of 102 subjects with a history of stroke or CHD and 45 subjects whose frozen blood samples were of insufficient quantity for the measurement of serum hs-CRP, the remaining 2589 individuals were enrolled 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.

Follow-Up Survey

The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. A detailed description of the study methods has been published previously.[3,13,15] In

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From the Department of Environmental Medicine (H.A., M.K., K.Y., T.N., Y.T., J.H., Y.K.) and the Department of Medicine and Clinical Science (Y.D., K.M., M.I.), Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Correspondence to Hisatomi Arima, MD, Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 Japan. E-mail harima@envmed.med.kyushu-u.ac.jp

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brief, the health status of any subject who had not undergone a regular examination or who had moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among 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 Departments of Pathology of Kyushu University. During the follow-up period, 545 subjects died, of whom 412 (75.6%) underwent autopsy. Only one participant was lost to follow-up.

Outcomes

The primary outcome of the present analysis was CHD. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction (MI), silent MI, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[3,14] Acute MI was diagnosed when a subject met at least 2 of the 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 electrocardiographic (ECG) changes; (4) morphological changes including local asynergy of cardiac wall motion on echocardiography, a persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. The secondary outcomes of the present investigation were deaths attributable to any cardiovascular disease (ICD-10[16] codes I00-I99), deaths attributable to noncardiovascular disease, and total deaths.

Risk Factors

Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was defined by a 75-g oral glucose tolerance test and by fasting (≥7.0 mmol/L) or postprandial (≥11.1 mmol/L) blood glucose levels or by the use of hypoglycemic agents. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically. Low-density lipoprotein (LDL) cholesterol level was estimated using the Friedewald formula.[17] Hypercholesterolemia was defined as a serum cholesterol level of 5.69 mmol/L or higher. Serum specimens collected at the time of CRP measurement were stored at −20°C until they were used in 2002. Serum hs-CRP levels were analyzed using a modification of the Behring latex-enhanced CRP assay on a BN-100 nephelometer (Dade Behring) with a 2% interassay coefficient of variation. Sitting blood pressure (BP) was measured 3 times at the right upper arm using a sphygmomanometer after 5 minutes of rest; an average of 3 measurements was used for the analysis. Hypertension was defined as BP levels of ≥140/90 mm Hg or current treatment with antihypertensive agents. The waist circumference was measured at the umbilical level in a standing position. Height and weight were measured in light clothes without shoes, and body mass index (BMI, kg/m^2) was calculated. Obesity was defined as a BMI of ≥25kg/m^2. ECG abnormalities were defined as Minnesota code 3-1 or 4-1,2,3. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire. Smoking habits and alcohol intake were classified as either current or not. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group. Metabolic syndrome was defined using criteria recommended in the National Cholesterol Education Program Adult Treatment Panel III guideline[18] with a modification of abdominal obesity, which was defined as a waist circumference ≥90 cm in men and ≥80 cm in women according to the International Obesity Task Force central obesity criteria for Asia.[19]

Statistical Analysis

We used quartiles of hs-CRP levels for the analysis of the effects of hs-CRP on the risks of CHD. The contributions of relevant factors to an elevated hs-CRP level, which was defined as the highest quartile, were examined using a logistic regression model, with an estimated odds ratio (OR) and 95% confidence interval (95% CI). The cumulative incidence of CHD was estimated using Cox's proportional hazards model. The incidence rates were calculated by the person-year method and standardized for age and sex distribution of the world standard population by the direct method using 10-year age groupings. The age- and sex-adjusted or multivariate-adjusted hazard ratio (HR) and 95% CI were estimated using Cox's proportional hazard model. Comparison of the effects hs-CRP between participants with and without other cardiovascular risk factors was done, and the probability value for homogeneity was estimated by adding an interaction term to the statistical model. All analyses were performed using the SAS software package (SAS Institute).

Results

Among the 2589 participants, the median hs-CRP level was 0.43 mg/L. The baseline characteristics of the subjects by hs-CRP quartile groups are shown in Table 1. Subjects with higher hs-CRP levels were older and less frequently women. The age- and sex-adjusted logistic regression analysis revealed that hypertension (OR, 1.40; 95% CI, 1.16 to 1.69), diabetes (OR, 1.67; 95% CI, 1.29 to 2.16), obesity (OR, 1.80; 95% CI, 1.47 to 2.22), hypercholesterolemia (OR, 1.32; 95% CI, 1.09 to 1.60), metabolic syndrome (OR, 2.04; 95% CI, 1.67 to 2.50), and smoking habits (OR, 1.96; 95% CI 1.56 to 2.47) were significantly associated with elevated hs-CRP levels, which were defined as the highest quartile (>1.02 mg/L).

During the 14 years of follow up, 129 coronary events were observed. The Figure shows the age- and sex-adjusted cumulative incidence of CHD according to hs-CRP quartiles. The cumulative incidence of CHD clearly increased with rising hs-CRP levels. The age- and sex-adjusted incidence rates of CHD according to hs-CRP quartiles are shown in Table 2. The incidence rates rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years from the first to the fourth quartile groups, respectively ($P<0.0001$ for trend). Table 2 also shows age- and sex-adjusted and multivariate-adjusted HRs and 95% CIs for the development of CHD according to the hs-CRP quartiles. The risks of CHD significantly increased with rising hs-CRP levels even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise ($P=0.0002$ for trend). The risk of CHD in the highest quartile group was significantly higher than that in the lowest group (multivariate-adjusted HR, 2.98; 95% CI, 1.53 to 5.82).

During the follow-up period, 545 participants died (158 died of cardiovascular disease and 387 died of noncardiovascular disease). The age- and sex-adjusted total and cause-specific mortality rates are shown in Table 3. The age-and sex-adjusted all-cause mortality rates rose progressively with higher hs-CRP levels ($P<0.0001$ for trend). The age- and sex-adjusted and multivariate-adjusted HRs also increased with rising hs-CRP levels even after controlling for other risk factors (Table 3; $P<0.0001$ for trend). When causes of death were divided into cardiovascular and noncardiovascular diseases, the relationship of hs-CRP to cardiovascular deaths was stronger than that to noncardiovascular deaths.

Age- and sex-adjusted hazard ratios of hs-CRP (highest versus lowest quartiles) for the development of CHD among

Table 1. Baseline Characteristics by Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Age, y	55 (11)	58 (12)	59 (11)	62 (12)	<0.0001
Women, %	64	63	55	51	<0.0001
Systolic blood pressure, mm Hg	128 (20)	132 (22)	136 (21)	138 (21)	<0.0001
Diastolic blood pressure, mm Hg	76 (11)	78 (11)	79 (11)	79 (12)	<0.0001
Hypertension,* %	29	39	45	52	<0.0001
ECG abnormalities,† %	15	15	16	18	0.1
Diabetes,‡ %	6	9	16	17	<0.0001
Waist, cm	77.4 (8.8)	80.6 (9.0)	83.8 (8.8)	83.8 (9.5)	<0.0001
Body mass index, kg/m^2	22 (3)	23 (3)	24 (3)	24 (3)	<0.0001
Total cholesterol, mmol/L	5.21 (1.02)	5.38 (1.09)	5.44 (1.11)	5.40 (1.13)	0.002
Triglycerides, mmol/L	1.15 (0.99)	1.37 (1.22)	1.56 (1.71)	1.48 (1.02)	<0.0001
HDL cholesterol, mmol/L	1.38 (0.30)	1.34 (0.31)	1.27 (0.29)	1.22 (0.30)	<0.0001
LDL cholesterol,§ mmol/L	3.30 (1.01)	3.41 (1.12)	3.46 (1.14)	3.50 (1.09)	0.0009
Metabolic syndrome, %	14	24	33	39	<0.0001
Current smoker, %	19	20	26	35	<0.0001
Current alcohol use, %	27	27	35	33	0.006
Regular exercise, %	10	9	9	12	0.2

Values are means (SD) or frequencies.

hs-CRP indicates high-sensitivity C-reactive protein; ECG, electrocardiographic; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.

†Minnesota codes 3-1 or 4-1,2,3.

‡Fasting glucose e ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.

§LDL cholesterol level was estimated using the Friedewald formula.

major clinical subgroups defined by the absence or presence of other cardiovascular risk factors are shown in Table 4. There were comparable effects of hs-CRP on the risk of CHD for participants who were and those who were not hypertensive (*P* homogeneity=0.7). Likewise, there were no clear differences in the effects of hs-CRP for participants with and without other cardiovascular risk factors such as diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits (all *P* homogeneity >0.4).

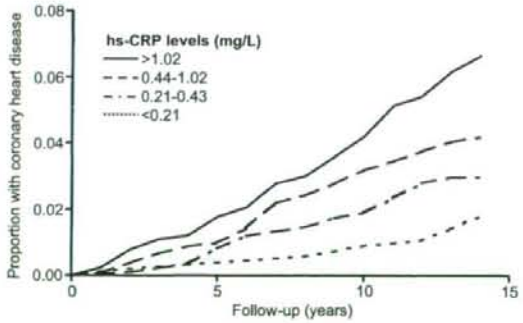

Figure. Age- and sex-adjusted cumulative incidence of coronary heart disease according to quartiles of high-sensitivity C-reactive protein. hs-CRP indicates high-sensitivity C-reactive protein.

Discussion

The present analysis demonstrated that serum hs-CRP levels were clearly associated with future coronary events in a general population of Japanese. The association between hs-CRP and CHD was strong and continuous down to very low hs-CRP levels of less than 0.21 mg/L. These associations remained strong even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, the effects of hs-CRP were comparable for subjects with and without other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, and smoking habits.

Large-scale nested case-control studies have reported that participants with incident CHD had higher levels of hs-CRP.[5,6,8–11] Likewise, large-scale cohort studies have clearly demonstrated that hs-CRP levels predicted future coronary events.[7,12] However, these studies were mainly conducted in Western populations, and it is unclear to what extent these associations apply to Japanese populations. The Honolulu Heart Program has reported a clear association between hs-CRP levels and the future development of CHD in a population of Japanese Americans.[20] The present analysis from the Hisayama Study confirmed the results from these previous observational studies in a general population of Japanese, finding that the relative risks of increasing hs-CRP levels for the development of CHD were similar to those

Table 2. Incidence Rates and Adjusted Hazard Ratios for Development of Coronary Heart Disease According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
No. of events/person-years	11/8589	22/8297	36/8073	60/7485	
Crude incidence rate (per 1000 person-years)	1.3	2.7	4.5	8.0	
Age- and sex-adjusted incidence rate (per 1000 person-years)	1.6	3.3	4.5	7.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.75 (0.85 to 3.61)	2.55 (1.30 to 5.02)	3.96 (2.07 to 7.57)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.60 (0.77 to 3.31)	1.97 (0.98 to 3.95)	2.98 (1.53 to 5.82)	0.0002

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

obtained from other observational studies conducted in Western populations[5–12] or in a population of Japanese Americans.[20] These findings suggest that hs-CRP is an important risk factor for CHD among Japanese as well as among Westerners.

In the present analysis, hs-CRP levels in Japanese (median 0.43 mg/L) were much lower than those in Western populations (median approximately 1.5 to 2.0 mg/L).[21,22] This is consistent with the findings of other cross-sectional studies in which Asian subjects had lower hs-CRP levels compared to Western subjects.[21–24] The reason for this ethnic difference is not clearly resolved, but genetic diversity has been reported to influence hs-CRP levels.[25] The relatively low BMI in Japanese and differences in diet and lifestyle may also have modulated hs-CRP levels.[26] The Honolulu Heart Program reported a median hs-CRP level of 0.54 mg/L among Japa-

Table 3. Mortality Rates and Adjusted Hazard Ratios for Total and Cause-Specific Deaths According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Total deaths					
No. of events/person-years	79/8624	106/8365	143/8181	217/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	12.7	15.2	18.9	23.5	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.08 (0.81 to 1.45)	1.30 (0.99 to 1.72)	1.80 (1.39 to 2.34)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.13 (0.84 to 1.51)	1.41 (1.06 to 1.87)	1.85 (1.41 to 2.43)	<0.0001
Cardiovascular deaths					
No. of events/person-years	16/8624	28/8365	47/8181	67/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	2.2	3.7	6.0	7.2	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.75 to 2.55)	2.15 (1.22 to 3.80)	2.77 (1.60 to 4.80)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.40 (0.75 to 2.60)	2.28 (1.27 to 4.09)	3.00 (1.70 to 5.28)	<0.0001
Noncardiovascular deaths					
No. of events/person-years	63/8624	78/8365	96/8181	150/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	10.5	11.5	12.9	16.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.00 (0.72 to 1.40)	1.09 (0.79 to 1.50)	1.55 (1.15 to 2.08)	0.0004
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.06 (0.76 to 1.48)	1.18 (0.85 to 1.64)	1.56 (1.14 to 2.13)	0.001

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 4. Age- and Sex-Adjusted Hazard Ratios of High-Sensitivity C-Reactive Protein (Highest vs Lowest Quartiles) for Development of Coronary Heart Disease Among Major Clinical Subgroups Defined by the Absence or Presence of Other Cardiovascular Risk Factors

	No. of Events/Person-Years			
	Highest Quartile (hs-CRP>1.02 mg/L)	Lowest Quartile (hs-CRP<0.21 mg/L)	Hazard Ratio* (95% CI)	*P* Homogeneity
Hypertension†				
Absent	18/3843	6/6224	3.18 (1.25 to 8.08)	0.7
Present	42/3643	5/2365	4.27 (1.68 to 10.82)	
Diabetes‡				
Absent	45/6276	9/8122	3.73 (1.81 to 7.68)	0.7
Present	15/1210	2/467	2.84 (0.65 to 12.43)	
Obesity§				
Absent	45/5113	10/7412	3.63 (1.81 to 7.28)	0.7
Present	15/2373	1/1177	5.42 (0.71 to 41.35)	
Hypercholesterolemia‖				
Absent	32/4448	5/5975	4.74 (1.83 to 12.26)	0.4
Present	28/3037	6/2614	2.83 (1.16 to 6.88)	
Metabolic syndrome¶				
Absent	27/4340	7/7068	3.34 (1.44 to 7.75)	1.0
Present	29/2631	3/1122	3.31 (1.00 to 10.92)	
Current smoking				
Absent	34/4910	9/7030	3.39 (1.61 to 7.15)	0.5
Present	26/2576	2/1559	5.94 (1.40 to 25.12)	

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.
*Hazard ratios for the highest vs the lowest quartile of high-sensitivity C-reactive protein.
†Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.
§Body mass index ≥25kg/m².
‖Total cholesterol ≥5.69 mmol/L.
¶Defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

nese Americans without CHD,[20] which was lower than that of Western populations but higher than that obtained from the present analysis. These findings suggest that lower hs-CRP levels among Asian populations are derived from differences in genetic factors as well as differences in BMI, diet, and lifestyle.

Another important finding obtained from the present analysis is that the association between hs-CRP levels and CHD was continuous from very low hs-CRP levels and that a slightly elevated hs-CRP level of more than 1 mg/L was clearly associated with increased risk of future coronary events in Japanese. Similar findings were obtained from the Honolulu Heart Program, whose subjects were Japanese American.[20] A low cut-off point of hs-CRP (<1 mg/L) has also been suggested as the target of lipid lowering therapy with statin for maximum reduction of recurrent coronary events or deaths among Western patients with acute coronary syndrome.[27–29] These findings imply that the association between hs-CRP and CHD are likely to be continuous down to very low hs-CRP levels among Asian as well as Western subjects. The American Heart Association and the Centers for Disease Control have recommended categorizing subjects using hs-CRP cut-off points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively, based mainly on the findings obtained from studies done in Western populations.[30] Among Asian subjects whose hs-CRP levels are much lower than those of Western subjects, however, an hs-CRP level of >1 mg/L is likely to be the cut-off point for the high-risk category.

In the present analysis, the effects of hs-CRP on the risks of future coronary events were independent of other cardiovascular risk factors and did not differ between participants with and those without traditional risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits. These results suggest that measurement of hs-CRP is likely to provide additional information for the detection of high-risk individuals among subjects without traditional risk factors as well as for the detection of extremely high-risk individuals among those with traditional risk factors. This finding is consistent with other observational studies suggesting that inclusion of hs-CRP into risk prediction models improves the accuracy of cardiovascular risk classification.[31,32]

Several limitations of our study should be discussed. The primary limitation is that we estimated the cut-off point of hs-CRP for detection of high-risk subjects based on analysis using quartile groupings despite continuous relationships between hs-CRP and the risks of CHD. The cut-off point

could change depending on the way of grouping the subjects or on the way of selecting the reference group. Given that this limitation might have overestimated the cut-off point, the true cut-off point for detection of high-risk subjects may be lower than 1 mg/L. A second limitation is that our findings are based on a 1-time measurement of serum hs-CRP, which may not accurately reflect the status of a study participant. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A third limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.[10] The last limitation is that our study lacked information on drug use at baseline and during the follow-up period. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.[33] However, these medications were rarely used in Japan in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings. It is also known that some medications have been shown to be beneficial for prevention of CHD, and high-risk individuals with higher hs-CRP levels were likely to receive these medications. Given that this limitation might have underestimated the association between hs-CRP and CHD, the true association may be stronger than that obtained from the present analysis.

In conclusion, the present analysis has clearly demonstrated that hs-CRP levels were associated with future coronary events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. High-risk approaches for the prevention of CHD using hs-CRP measurement are likely to provide additional protection against the burden of CHD in Japan.

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Disclosures

None.

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Original Article

Arterial Stiffness and QT Interval Prolongation in a General Population: The Hisayama Study

Daisuke MAEBUCHI[1], Hisatomi ARIMA[1], Toshiharu NINOMIYA[1], Koji YONEMOTO[1], Michiaki KUBO[1], Yasufumi DOI[2], Yumihiro TANIZAKI[2], Kiyoshi MATSUMURA[2], Mitsuo IIDA[2], and Yutaka KIYOHARA[1]

Few population studies have addressed the association of QT interval prolongation with clinical or subclinical arterial disease. The primary objective here was to examine the relationship between the pulse wave velocity (PWV) and the heart rate–corrected QT interval duration (QTc). This is a cross-sectional study, based on a survey of a general population of Japanese. We examined 2,666 community-dwelling individuals without history of cardiovascular disease, aged 40 or over. The PWV was measured between the brachial and ankle regions (baPWV). QTc was estimated using Bazett's equation. The age-adjusted mean values of QTc increased progressively with rising baPWV levels for either sex: for men, 397, 401, 403, and 406 ms for quartile groups defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s, respectively ($p<0.0001$ for trend); for women, 406, 410, 414, and 417 ms for quartile groups defined by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s, respectively ($p<0.0001$ for trend). When male and female subjects were combined, this positive relationship between baPWV and QTc remained significant, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium, alcohol intake, and smoking habits ($p<0.0001$ for trend). In conclusion, baPWV is independently associated with QT interval prolongation. (*Hypertens Res* 2008; 31: 1339–1345)

***Key Words*: pulse wave velocity, QT interval duration, epidemiology**

Introduction

The QT interval duration on an ECG represents the duration of ventricular depolarization and repolarization (*1*, *2*). It has been suggested that disturbance of cardiac ion channels (*1*, *2*), decreased autonomic tone (*3*), and myocardial ischemia/infarction (*4*) extend the QT interval duration, but the etiology of the acquired form of QT interval prolongation has not been clearly defined. Recently, several epidemiological studies have shown that QT interval prolongation predicts the risks of clinical arterial disease (*5–9*) as well as sudden cardiac death (*5*). Likewise, a few cross-sectional studies have suggested a positive association between QT interval prolongation and subclinical arterial disease, such as carotid intima media thickness (*10–12*). However, there is significant uncertainty about the association between QT interval prolongation and other forms of subclinical arterial disease.

From the [1]Department of Environmental Medicine and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

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Address for Reprints: Hisatomi Arima, M.D., Ph.D., Yutaka Kiyohara, M.D., Ph.D., Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Maidashi 3–1–1, Higashi-ku, Fukuoka 812–8582, Japan. E-mail: harima@envmed.med.kyushu-u.ac.jp; kiyohara@envmed.med.kyushu-u.ac.jp

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Table 1. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,089 Men

Variables	Brachial-ankle pulse wave velocity (cm/s)				*p* for trend
	963–1,369 (*n*=270)	1,370–1,560 (*n*=273)	1,561–1,840 (*n*=276)	1,841–3,690 (*n*=270)	
Age (years)	51.4±8.4	55.6±9.6	60.2±9.7	68.9±8.9	<0.0001
Heart rate (bpm)	60.1±9.9	63.4±9.9	65.2±10.0	70.4±9.9	<0.0001
Systolic blood pressure (mmHg)	116.4±16.4	126.9±14.9	138.9±15.0	151.2±16.4	<0.0001
Diastolic blood pressure (mmHg)	71.1±9.9	78.6±9.9	84.6±10.0	91.2±9.9	<0.0001
Hypertension (%)	11.8	29.4	60.8	89.5	<0.0001
Antihypertensive drugs (%)	5.1	13.6	22.2	21.2	<0.0001
β-Blocker (%)	2.3	2.8	5.7	3.5	0.15
Calcium channel blocker (%)	4.3	9.3	20.7	16.5	<0.0001
ACE inhibitor (%)	0.9	2.8	5.0	5.1	0.0014
ARB (%)	1.8	5.6	3.0	4.1	0.65
ECG abnormalities (%)	11.5	14.5	17.4	18.9	0.001
Total cholesterol (mmol/L)	5.0±0.9	5.0±0.9	5.1±0.9	5.1±0.9	0.23
HDL cholesterol (mmol/L)	1.5±0.4	1.5±0.4	1.4±0.4	1.5±0.4	0.46
LDL cholesterol (mmol/L)	3.1±0.9	3.1±0.8	3.0±0.8	3.0±0.9	0.25
Triglyceride (mmol/L)	1.3±1.4	1.5±1.3	1.9±1.3	1.9±1.5	<0.0001
Dyslipidemia (%)	46.6	50.5	55.4	59.8	0.002
Fasting plasma glucose (mmol/L)	5.8±1.5	6.1±1.4	6.3±1.3	6.7±1.5	<0.0001
HbA1c (%)	4.9±0.8	5.0±0.8	5.1±0.8	5.3±1.0	<0.0001
Diabetes (%)	12.6	15.0	20.5	43.7	<0.0001
BMI	23.0±3.3	23.4±3.3	23.8±3.3	23.8±3.3	0.01
Obesity (%)	30.2	29.5	32.0	53.2	0.09
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.10
Serum potassium (mmol/L)	4.4±0.3	4.4±0.3	4.3±0.3	4.3±0.3	0.08
Alcohol intake (%)	65.7	65.1	74.2	75.5	0.0006
Habitual smoking (%)	55.7	45.1	45.1	37.3	0.04

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Aortic pulse wave velocity (PWV) is an established marker for subclinical arterial disease (*13*, *14*) as well as for arterial stiffness (*15*). Brachial-ankle PWV (baPWV) has also been shown to be closely associated with aortic PWV and to be an excellent functional marker for subclinical arterial disease (*16*).

The present cross-sectional study evaluates the association of baPWV with heart rate–corrected QT interval duration (QTc) in a general population of Japanese.

Methods

Study Population

The Hisayama Study is an ongoing population-based epidemiological study designed to investigate the morbidity and mortality of cardiovascular disease and its risk factors in the town of Hisayama, Japan. The design of the Hisayama Study has been described in detail elsewhere (*17*). The present cross-sectional study was based on a screening survey conducted in 2002 and 2003. A total of 3,328 residents aged 40 years or over (77.6 % of the total population of this age group) participated in the examination and underwent a comprehensive assessment including baPWV and ECG. Of these, 242 subjects for whom there was no information on baPWV or ECG, 54 subjects who were likely to have peripheral arterial disease (ankle-brachial index <0.9), 189 subjects with atrial fibrillation or intraventricular conduction disturbance (QRS interval >120 ms), 30 subjects with elevated heart rate (>100 beats/min), 22 subjects who did not take a fasting blood test, 16 subjects taking medication affecting the QT interval duration (*i.e.*, antiarrhythmic drugs, antibiotics, antipsychotic agents or antihistamines) (*2*), 111 subjects with a history of cardiovascular disease (myocardial infarction, coronary revascularization or stroke), and 30 subjects who refused to participate in the present study were excluded from the analyses. The final study group comprised 2,666 subjects (1,089 men and 1,577 women).