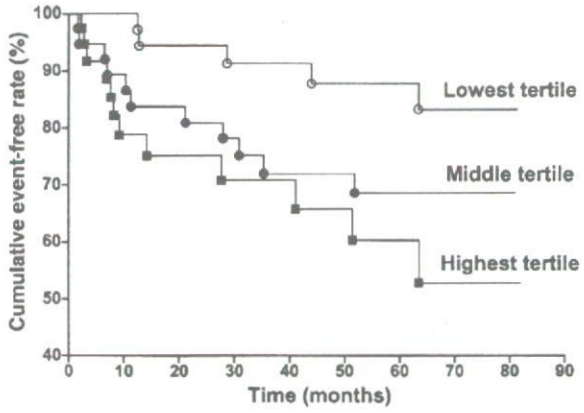

Fig. 1 – CV event-free curves obtained with the Kaplan–Meier method in the three groups divided by tertiles of basal AM levels. Cumulative event-free rates in the lowest, middle, and highest tertiles were 83.2%, 68.6%, and 52.8%, respectively (log-rank test, $P = 0.033$). Lowest tertile, basal AM <10.1 fmol/mL ($n = 40$); middle tertile, basal AM ≥10.1 and <13.1 fmol/mL ($n = 40$); highest tertile, basal AM ≥13.1 fmol/mL ($n = 41$).

Cox regression analysis was performed to examine the predictive power of plasma AM for future CV events, comparing with those of hs-CRP and adiponectin. In the univariate analysis, past history of coronary artery disease, creatinine clearance, and plasma hs-CRP in addition to plasma AM were significantly related to the incidence of CV events during the follow-up periods (Table 4). Among these possible predictive factors, high plasma AM and low creatinine clearance were independent predictors of CV events in the multivariate analysis, and the predictive value of AM for morbidity was most significant (+10% per 1-fmol/mL increase in AM, $P = 0.004$). Furthermore, even when the multivariate regression was reanalyzed after excluding subjects with previous coronary artery disease, the predictive value of AM for CV events was still significant, independently of creatinine clearance and other variables (hazard ratio 1.20 (per 1 fmol/mL increase), 95% confidence interval 1.06–1.35, $P = 0.004$).

4. Discussion

Plasma AM levels are known to be elevated in various pathological states, including several CV diseases [7,8,11, 15,17,22,24,25,40,41]. In addition, some studies showed that AM level was a predictor of survival in patients with acute myocardial infarction and chronic heart failure [12,23,29,30]. However, there have been no reports examining whether plasma AM can predict the occurrence of CV events in subjects with CV risk factors. Thus, the present study has demonstrated for the first time that an increased level of plasma AM becomes a significant predictor of future CV events in high-risk patients, independently of a variety of influencing factors.

In this study, we compared the predictive power of AM with those of hs-CRP and adiponectin. Our findings showed that neither hs-CRP nor adiponectin was an independent

Table 4 – Predictors of future CV events by univariate and multivariate Cox regression analysis

	Hazard ratio (95% CI)	P
Univariate analysis		
Age, 10 years	1.34 (0.88–2.04)	0.174
Sex, male	1.13 (0.50–2.56)	0.772
Body mass index, 1 kg/m^2	0.97 (0.88–1.07)	0.523
Hypertension, yes	2.02 (0.61–6.71)	0.249
Diabetes mellitus, yes	1.90 (0.89–4.06)	0.097
Hyperlipidemia, yes	1.00 (0.47–2.11)	0.999
Smoking (current or past), yes	1.65 (0.63–4.33)	0.313
Previous coronary artery disease, yes	2.90 (1.31–6.43)	0.009
Systolic blood pressure, 10 mmHg	1.03 (0.83–1.27)	0.799
Diastolic blood pressure, 10 mmHg	0.90 (0.65–1.24)	0.509
Heart rate, 5 beats/min	1.02 (0.83–1.27)	0.828
Fasting plasma glucose, 10 mg/dL	1.07 (0.97–1.19)	0.196
Hemoglobin A1c, 1%	1.14 (0.96–1.36)	0.126
Total cholesterol, 10 mg/dL	0.90 (0.80–1.02)	0.102
Triglycerides, 10 mg/dL	1.00 (0.94–1.07)	0.960
HDL cholesterol, 5 mg/dL	1.02 (0.90–1.16)	0.769
Creatinine clearance, 10 mL/min	0.80 (0.70–0.93)	0.003
AM, 1 fmol/mL	1.13 (1.06–1.19)	<0.001
Hs-CRP, 0.1 mg/dL	1.08 (1.00–1.18)	0.047
Adiponectin, 1 μg/mL	1.08 (0.99–1.16)	0.054
Multivariate analysis		
Creatinine clearance, 10 mL/min	0.87 (0.76–0.99)	0.043
AM, 1 fmol/mL	1.10 (1.03–1.18)	0.004

CI: confidence interval. In the multivariate analysis using stepwise regression model, all factors that had a significant association in the univariate analysis, i.e., previous coronary artery disease, creatinine clearance, AM, and hs-CRP, were included as possible independent variables.

predictor of future CV events, in contrast to the powerful prognostic value of AM. Several large epidemiological studies have suggested that CRP measurement predicts the risk of future CV events [1,31–34,36], whereas others have failed to identify CRP as a significant independent risk factor, especially after using multivariate analysis [28,42,44]. Hs-CRP was one of the significant predictors of CV events in univariate Cox regression analysis of the present study. However, since there was a close correlation between hs-CRP and AM levels (data not shown) and the predictive power of hs-CRP was weaker than that of AM in univariate analysis, hs-CPR might not become an independent predictor in multivariate analysis. As for adiponectin, it has been shown that low levels of plasma adiponectin are a predictor of CV events and mortality [4,5,9,16,37,47], but some studies reported that adiponectin did not predict future risk of coronary artery disease after adjusted for classical risk factors [18,35]. In addition, recent studies revealed that high, rather than low, adiponectin levels were associated with increased mortality and incidence of myocardial infarction in patients with chronic heart failure, chronic kidney disease, and stable angina [2,13,21]. Thus, the value of adiponectin as an independent risk marker for CV events and mortality remains controversial at present.

Although the exact reason behind the superiority of plasma AM over hs-CRP and adiponectin as a predictor of CV events in the present study remains to be elucidated, a number of mechanisms may be involved. AM is produced in various organs and tissues, but the main source of circulating AM is the blood vessels (especially vascular endothelial cells) [38], in contrast to the major sites of the production of CRP and adiponectin. Therefore, AM may directly reflect vascular inflammation and endothelial injury during the initiation and development of atherosclerosis. In fact, increased plasma levels of AM were reported to be associated with the progression of atherosclerotic lesions [7,40]. Furthermore, since several studies have shown that ischemic and hypoxic conditions stimulate the production and secretion of AM [26,43,46], it is possible that the increase in baseline AM might be induced by silent cerebral or cardiac ischemia before attack. Plasma AM has also been shown to increase in response to left ventricular systolic and diastolic dysfunction [23,25,45], suggesting the possibility that baseline AM in our subjects could detect latent cardiac disorders. Therefore, as AM comprehensively reflects vascular inflammation and injury, atherosclerotic change, systemic and myocardial ischemia, and cardiac dysfunction, plasma AM might become a sensitive marker of future CV disease.

There were some limitations in the present study. The sample size of our subjects was small to evaluate the predictive power of AM discretely for cerebrovascular, coronary, and heart failure events. In addition, the prognostic value of AM for all-cause and CV death could not be investigated. As another limitation of this study, we did not consider the influence of medication during follow-up on the occurrence of CV disease. Therefore, the use of statin, aspirin, renin angiotensin system inhibitors, and β-blockers and the alteration of dosage of these drugs after the initial assessment might bias the outcome of the present study. Furthermore, we did not examine the change of plasma AM levels during follow-up periods. It is possible that the prognostic potential of AM may be raised by serially evaluating its plasma level in high-risk patients.

In conclusion, the present findings indicate that plasma AM is a powerful independent predictor of future CV events in patients with multiple CV risk factors, and suggest that its prognostic value is superior to that of hs-CRP or adiponectin. However, further investigations using larger population of high-risk patients will be required to establish the usefulness of AM as a novel predictive marker for CV diseases.

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Fasting Plasma Glucose Cutoff for Diagnosis of Diabetes in a Japanese Population

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Objective: We examined the relationship between fasting plasma glucose (FPG) and 2-h post-load glucose (PG) levels, and the optimal FPG cutoff level to correspond to a 2-h PG of 11.1 mmol/liter, the gold standard diagnostic criterion, in a general Japanese population.

Design: Cross-sectional study populations of 2421 subjects in 1988 and 2698 subjects in 2002, aged 40–79 yr and without antidiabetic medication, were tested with an oral glucose tolerance test. The relationship between FPG and 2-h PG was investigated by various regression models and a receiver operating characteristic curve.

Results: The best-fit model for the relationship between FPG and 2-h PG was a quadratic regression model. The FPG cutoff levels corresponding to the 2-h PG of 11.1 mmol/liter by this model were 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002. In the combined populations, the FPG cutoff point was 6.3 mmol/liter; the sensitivity and specificity of this cutoff point for detecting a 2-h PG of 11.1 mmol/liter were 75.2 and 88.6%, respectively. The receiver operating characteristic curve analysis confirmed that the corresponding FPG point was 6.2 mmol/liter in both the 1988 and 2002 populations. In a stratified analysis, the FPG cutoff level increased with increasing body mass index levels; however, even in subjects with body mass index more than or equal to 30 kg/m^2, the FPG cutoff level was lower than 7.0 mmol/liter.

Conclusions: Our findings suggest that the FPG cutoff level corresponding to the 2-h PG of 11.1 mmol/liter in the general Japanese population is lower than the current diagnostic criterion. (***J Clin Endocrinol Metab*** **93: 3425–3429, 2008)**

A 2-h post-load glucose (PG) cutoff level of 11.1 mmol/liter is considered to be the gold standard diagnostic criterion for diabetes mellitus. This cutoff point was originally adopted for several reasons (1). First, 11.1 mmol/liter has been found to approximate the cutoff point separating the two components of the bimodal distribution of 2-h PG levels. Second, according to several epidemiological studies, including our own, the prevalence of microvascular disease sharply increases in patients having a 2-h PG above 11.1 mmol/liter (1–4). Third, a great number of clinical and epidemiological studies have used this criterion. By contrast, fasting plasma glucose (FPG) has not been adequately justified as a diagnostic criterion. The FPG cutoff point for diagnosing diabetes was revised by the Expert Committee of the American Diabetes Association (ADA) (1) in 1997; namely, the cutoff point defining diabetes was reduced from more than or equal to 7.8 mmol/liter to more than or equal to 7.0 mmol/liter, though the ADA itself has recognized that this new cutoff point is not the best equivalent of the 2-h value of 11.1 mmol/liter (1, 5). The World Health Organization adopted an FPG of 7.0 mmol/liter as a diagnostic criterion of diabetes in 1998 (6). This lowering was based on the following findings from several studies, primarily with cohorts of high body mass index (BMI) subjects: 1) the prevalence and incidence of diabetic retinopathy increased at an FPG of approximately 7.0 mmol/liter (1, 3, 4); 2) the discrepancy in the detection rate of diabetes between FPG and 2-h PG values was reduced when an FPG of 7.0 mmol/liter was

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Abbreviations: ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, post-load glucose; ROC, receiver operating characteristic.

used; and 3) the prevalence of diabetes by a 2-h PG cutoff point of 11.1 mmol/liter was identical to that of an FPG of approximately 7.0 mmol/liter in several populations. However, the Diabetes Prevention Program Research Group has recently shown that the retinopathy characteristic of diabetes was present in persons whose FPG was below the diabetic range and who had no known history of diabetes (7). Furthermore, an integrated study of three general populations suggested that although the prevalence of retinopathy increased with FPG concentration, there was no clear diagnostic cutoff (8). These findings imply that data of diabetic retinopathy alone are not adequate to determine an FPG cutoff point. Thus, another approach, such as a regression analysis, is needed to validate the FPG cutoff point.

On the other hand, it remains controversial whether the FPG of 7.0 mmol/liter is adequately diagnostic for diabetes in Asian populations, which tend to be leaner than Western populations. For instance, FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter were also lower than 7.0 mmol/liter in other Asian populations (9–11). There have been very few reports on this issue in the Japanese population, in which the prevalence of diabetes has been increasing rapidly in recent years. The purposes of this study were to determine the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter, and to check whether this cutoff value varied according to changes in the society over time by examining the relationship between FPG and 2-h PG values in a general Japanese population at two different time points separated by an interval of 14 yr.

Subjects and Methods

A population-based prospective study of cardiovascular disease has been underway since 1961 in the Town of Hisayama, a suburb in the Fukuoka metropolitan area on Kyushu Island, in Japan. Based on data from the national census, the age and occupational distributions for Hisayama have been almost identical to those of Japan as a whole from 1961 to the present. As a part of the study, two cross-sectional diabetes surveys of Hisayama residents were conducted in similar fashion in 1988 and 2002. A detailed description of the surveys has been published previously (12, 13); briefly, of the total of 3227 residents in 1988 aged 40–79 yr in the town registry, 2587 (participation rate, 80.2%) consented to take part in a comprehensive assessment, including a 75-g oral glucose tolerance test (OGTT) and an interview covering both medical histories (including items on diabetes, hypertension, and other chronic diseases) and current medical treatments with insulin and oral hypoglycemic agents. After excluding participants who had already had breakfast, those who were receiving insulin therapy for diabetes, and those who refused the OGTT due to complaints of nausea or general fatigue during the ingestion of glucose, we successfully completed the OGTT on 2480 subjects. An additional 59 subjects were excluded because they were taking oral hypoglycemic agents; thus, the final 1988 study group comprised 2421 subjects (1045 men and 1376 women) (Fig. 1). In 2002, we established another study population of 2698 (1162 men and 1536 women) using the same methods and criteria.

In both the 1988 and 2002 surveys, clinical evaluation and laboratory measurements were performed in a similar manner. The study subjects underwent the OGTT between 0800 and 1030 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h post-load, and was separated into plasma and blood cells within 20 min. Plasma glucose levels were determined by the glucose-oxidase method. The between-assay and within-assay coefficients of variance of glucose measurement in our laboratory were 0.96 and 0.81% at 5.6 mmol/liter, and 0.81 and 0.56% at 16.7 mmol/liter, respectively. Total cholesterol and triglycerides were determined enzymatically. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the average values were used in the analyses. Hypertension was defined as systolic blood pressure more than or equal to 140 mm Hg and/or diastolic blood pressure more than or equal to 90 mm Hg and/or current treatment with antihypertensive agents. The height and weight of each subject, wearing light clothes without shoes, were recorded, and the BMI (kg/m^2) was calculated. The interview investigated smoking habits and alcohol intake. Both were classified as either currently habitual or not. Subjects engaging in sports at least three times per week during their leisure time were classified into a regular exercise group.

SAS (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. Various regression models, including linear, quadratic, logarithmic, inverse, power, and exponential models, without covariates were examined to determine which best fit the relationship between FPG and 2-h PG levels. Furthermore, an FPG cutoff point corresponding to the 2-h PG of 11.1 mmol/liter was calculated from each regression equation. The sensitivity of the FPG cutoff point was defined as its ability to identify correctly individuals who had a 2-h PG of 11.1 mmol/liter or higher, and the specificity was its ability to identify correctly individuals who did not have a 2-h PG of 11.1 mmol/liter or higher. To compare the ability of FPG measurements to detect the presence or absence of a 2-h PG of 11.1 mmol/liter or higher across a range of values, we plotted receiver operating characteristic (ROC) curves. The diagnostic properties of specific cutoff levels of FPG were defined by maximizing the sensitivity and specificity to identify a 2-h PG of 11.1 mmol/liter or higher.

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the participants.

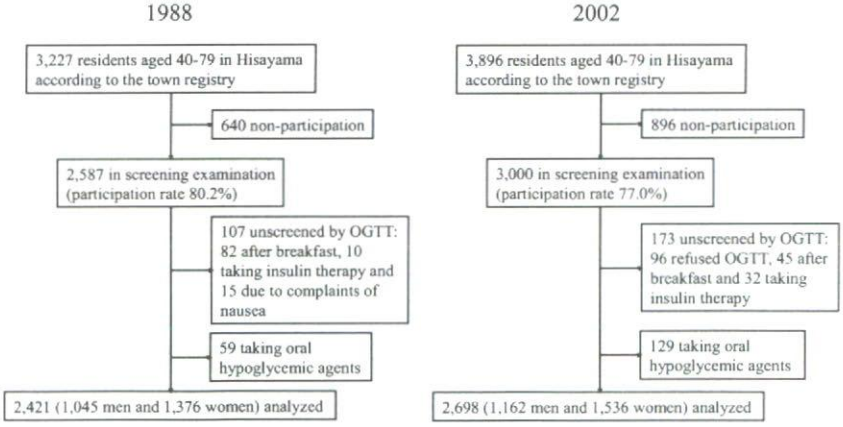

FIG. 1. Flow diagram of the study.

Results

The clinical characteristics of the subjects in 1988 and 2002 are summarized in Table 1. Mean values of age, FPG, 2-h PG, and BMI were higher in 2002 than 1988, whereas the frequency of men was not different between the populations.

To elucidate the relationship between FPG and 2-h PG, we analyzed their interrelationships using the various regression models listed in Table 2. FPG values corresponding to a 2-h PG of 11.1 mmol/liter and R^2 values were calculated for the combined populations

TABLE 1. Clinical characteristics of subjects: the Hisayama study in 1988 and 2002

	1988 (n = 2421)	2002 (n = 2698)	*P* value
Age (yr)	57 (10)	59 (11)	<0.001
Men (%)	43.2	43.1	0.94
FPG (mmol/liter)	5.7 (1.1)	6.0 (1.0)	<0.001
2-h PG (mmol/liter)	7.3 (3.2)	7.7 (3.1)	<0.001
BMI (kg/m^2)	23.0 (3.1)	23.3 (3.3)	<0.001

Values are means (SD).

of 1988 and 2002. The R^2 value was larger for the quadratic regression model, indicating that it is a better fit than the other models; the relevant FPG point in this model was 6.3 mmol/liter.

Figure 2 depicts the relationship between the FPG and 2-h PG in 1988 and 2002 considered separately. The quadratic model analyses were still the best fit among the various models for both the 1988 and 2002 populations (data not shown), with R^2 values of 64.0 in 1988 and 61.3 in 2002. The FPG point corresponding to a 2-h PG of 11.1 mmol/liter was 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002.

To confirm the cutoff point of FPG corresponding to the 2-h PG of 11.1 mmol/liter, we plotted ROC curves and calculated the optimal cutoff points defined as the maximum combination of sensitivity and specificity, and their area under the ROC curves (Fig. 3). In the 1988 subjects, the corresponding FPG point was 6.2 mmol/liter. The sensitivity and specificity of this cutoff point were 81.2 and 88.7%, respectively; and the area under the curve was 91.0%. In the 2002 subjects, the cutoff point was 6.2 mmol/liter; the sensitivity, specificity, and area under the curve were 77.9, 81.3, and 86.7%, respectively.

Finally, we performed a stratified analysis by sex, age, and BMI levels in the combined population using both the quadratic regression model and ROC analysis (Table 3). The FPG level corresponding to the 2-h PG of 11.1 mmol/liter was slightly higher in men than women by both the quadratic regression model and ROC analysis. Higher FPG levels corresponding to a 2-h PG of 11.1 mmol/liter were observed in the younger age groups in the quadratic regression model analysis. However, in ROC analysis there was no association between age and FPG level. The FPG level corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels in both the quadratic regression model and ROC analysis. However, even in subjects with a BMI more than or equal to 30 kg/m^2, the FPG cutoff level was still lower than the diagnostic criterion of 7.0 mmol/liter.

Discussion

We examined the association between FPG and 2-h PG levels in a general Japanese population at two time points separated by a 14-yr interval, and using the quadratic model, which proved to be the best fit for the data, demonstrated that the FPG level corresponding to a 2-h PG of 11.1 mmol/liter, the gold standard for diagnosis of diabetes, was 6.2 mmol/liter for the 1988 data and 6.3 mmol/liter for the 2002 data. The FPG points derived from the ROC analyses corroborated these findings. It has been reported that the corresponding FPG cutoff level by the quadratic model was 5.7 mmol/liter in Chinese (9) and 6.3 mmol/liter in Taiwanese (10). Together with the findings of these other studies, our results suggest that, in relatively lean Asian populations, including the Japanese, the FPG cutoff level is clearly lower than the FPG value of 7.0 mmol/liter, which is currently used in various diagnostic criteria for diabetes (1, 6), and that this situation did not change over the course of 14 yr in the Japanese population.

Although a method using FPG values corresponding to the gold standard of 2-h PG levels for diagnosis of diabetes has not yet been established, regression analysis appears to be a useful method for detecting the FPG cutoff value. Two previous epidemiological studies determined FPG cutoff points by analyzing the relationship between FPG and 2-h PG using linear or exponential models (14, 15). However, in our study the quadratic model showed the highest positive correlation between FPG and 2-h PG, and, thus, was the best-fitted model. This is consistent with the findings of studies in Taiwanese (9) and Chinese (10) populations.

The ADA recommends the use of the FPG instead of 2-h PG for diagnosing diabetes because it is difficult to perform an OGTT in routine clinical practice (1). Thus, it is very important to determine the appropriate FPG cutoff value for the diagnosis of diabetes in different populations. The FPG of 7.0 mmol/liter for diagnosing diabetes is based on several population studies examining the relationship between the glycemic threshold and diabetic retinopathy (1, 3, 4); however, optimal cutoff levels of plasma glucose for defining diabetes depend on ethnicity. In a Pima Indian study, the ROC curve analysis in a diabetic retinopathy study identified the optimal FPG cutoff level as 6.8 mmol/liter (3). The National Health and Nutrition Examination Survey III study of the U.S. population also reported that the prevalence of retinopathy increased dramatically at FPG levels of 6.7 mmol/liter (1). These findings were apparently confirmed by a similar study in Egypt (4), in which the optimal FPG cutoff level

TABLE 2. Relationship between FPG (Y) and 2-h PG (X) in various regression models for the combined population of 1988 and 2002

Model	Equation	FPG corresponding to 2-h PG of 11.1 mmol/liter (mmol/liter)	R^2 (%)
Quadratic	$Y = 0.0149X^2 - 0.102X + 5.621$	6.3	62.3
Linear	$Y = 0.243X + 4.024$	6.7	51.8
Exponential	$Y = 2.718^{(0.0323X + 1.511)}$	6.5	48.6
Power	$Y = 3.512X^{0.255}$	6.5	36.6
Logarithmic	$Y = 1.831 \log X + 2.277$	6.7	35.6
	$\text{Log}(Y) = 0.255 \log X + 1.256$	6.5	36.6
	$\text{Log}(Y) = 0.243 (\log X)^2 - 0.748 \log X + 2.260$	6.5	50.2
Inverse	$Y = 7.265 - 9.416/X$	6.4	20.1

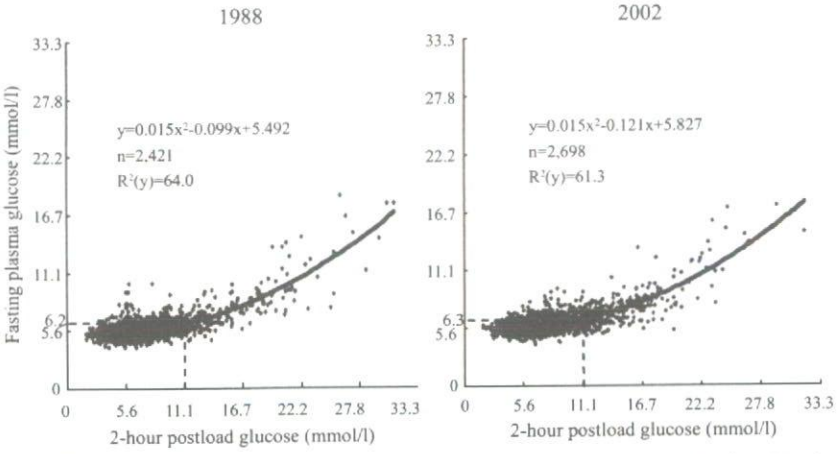

FIG. 2. The relationship between FPG and 2-h PG by a 75-g OGTT in Hisayama residents aged 40–79 yr in 1988 (*left panel*) and 2002 (*right panel*). *Solid line* represents the regression line by the quadratic regression model.

for detecting diabetic retinopathy was 6.9–7.2 mmol/liter. However, these three populations have higher BMI levels compared with Asian populations. We previously reported that although the glycemic threshold of 2-h PG for retinopathy in Japanese was 11.1 mmol/liter, that of FPG was only 6.4 mmol/liter (2). Other Asian population studies have reported optimal FPG cutoff levels for retinopathy ranging between 5.6 and 6.0 mmol/liter (16, 17). These findings suggest that FPG cutoff levels are lower in Asian populations than in other populations.

In our subjects the FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels. However, even in subjects with a BMI more than or equal to 30 kg/m^2, the FPG cutoff level using the quadratic model was 6.4 mmol/liter, much lower than the diagnostic criterion of 7.0 mmol/liter. It is not clearly understood why FPG cutoff levels differ among ethnic groups. One possible explanation is that the capacity for acute insulin response to glucose load may influence the FPG cutoff level. The acute insulin response is known to be lower in Asian populations than other populations (18). In some clinical studies, the loss of acute insulin response by somatostatin was associated with a marked impairment in the initial suppression of hepatic glucose production, which led to higher 2-h PG concentrations (19, 20). Thus, impairment of acute insulin response may lead to a wide gap between FPG and 2-h PG; in other words, much lower FPG cutoff levels correspond to the 2-h PG diagnostic standard level. These findings might explain why the FPG cutoff level for the diagnosis of diabetes is lower in Asian populations, including ours, even in those with high BMI.

In the present study, the R^2 value in the quadratic model and the sensitivity, specificity, and area under the curve in the ROC analysis were all lower in 2002 than 1988. Although this phenomenon was not clearly understood, one possible reason may be that individuals in 2002 had more diverse lifestyles compared with those in 1988. Nevertheless, it is noteworthy that the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter was similar in the two populations.

Two limitations of our study should be discussed. First, in our study we determined the FPG cutoff level that corresponded to a 2-h PG of 11.1 mmol/liter, the gold standard for the diagnosis of diabetes, rather than that corresponding directly to diabetic complications. However, our previous study showed that the glycemic threshold of FPG for retinopathy is 6.4 mmol/liter (2), a result very similar to that of the present study. These findings suggest that the quadratic model precisely predicts the relationship between FPG and 2-h PG levels, making the FPG cutoff level nearly as accurate as the 2-h PG level, as well as more useful in clinical settings. Second, it is known that 2-h PG values in a 75-g OGTT have lower reproducibility than FPG (21, 22). It might be reasonable to propose FPG as the "gold standard." However, in the National Health and Nutrition Examination Survey III, 2-h PG was more specific for diabetic retinopathy than FPG (1). In several epidemiological studies, 2-h PG was also a stronger predictor of cardiovascular disease and total death compared with FPG (23–27). In addition, a 2-h PG of 11.1 mmol/liter was established in some revised processes for the diagnosis of diabetes. Based on these studies, then, a 2-h PG of 11.1 mmol/liter remains the "gold standard." Nevertheless, the present study found that two cross-sectional populations in 1988 and 2002 had nearly the same cutoff FPG values. This suggests that the high variability in 2-h PG values did not invalidate the present findings.

In conclusion, we have shown that the quadratic regression model is best fitted for the relationship between FPG and 2-h PG in a general Japanese population. The FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/liter was 6.3 mmol/liter, and this result did not change over the course of 14 yr. Furthermore, the FPG cutoff levels were higher in subjects with higher BMI levels. The findings of the present study together with those of previous studies examining diabetic retinopathy sug-

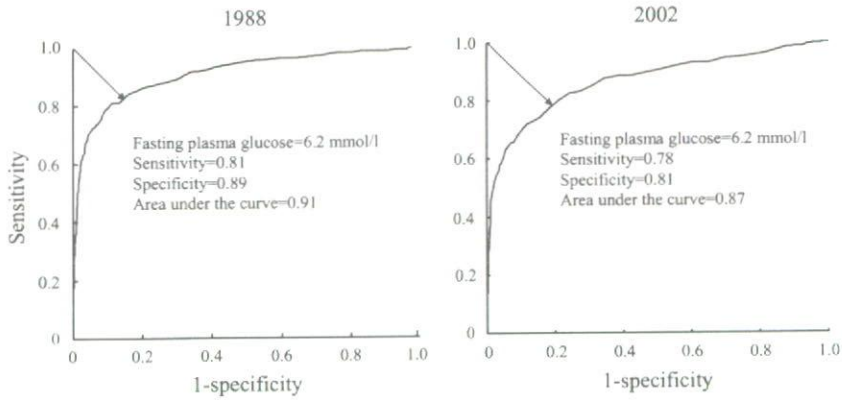

FIG. 3. ROC curves for FPG for predicting the 2-h PG of 11.1 mmol/liter using 1988 (*left*) and 2002 (*right*) data sets. The *arrow* shows the optimal cutoff point for detecting the 2-h PG of 11.1 mmol/liter defined as the maximum combination of sensitivity and specificity.

TABLE 3. FPG cutoff points corresponding to the 2-h PG of 11.1 mmol/liter by quadratic regression model and receiver operating curve analysis in the combined population of 1988 and 2002

Factors	No.	Cutoff point defined by quadratic regression analysis (mmol/liter)	Cutoff point defined by ROC analysis (mmol/liter)
Sex			
Men	2207	6.4	6.3
Women	2912	6.3	6.1
Age (yr)			
40–49	1341	6.4	6.0
50–59	1569	6.4	6.2
60–69	1363	6.3	6.2
70–79	846	6.2	6.1
BMI (kg/m^2)			
<20	818	6.1	5.9
20–24.9	2978	6.3	6.1
25–29.9	1192	6.3	6.2
≥30	131	6.4	6.7

gest that in Asian populations, the FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/liter is lower than 7.0 mmol/liter, the current diagnostic criterion for diabetes. Considering the growing importance of the FPG test in screening for diabetes, further investigations are required to clarify the optimal FPG cutoff level in Asian and other ethnic populations.

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

The Hisayama Study

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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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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).

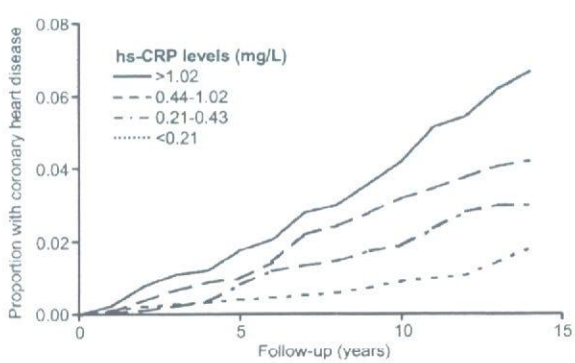

Figure. Age- and sex-adjusted cumulative incidence of coronary heart disease according to quartiles of high-sensitivity C-reactive protein. hs-CRP indicates high-sensitivity C-reactive protein.

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/m^2.
‖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

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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.

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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).

Table 2. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,577 Women

Variables	Brachial-ankle pulse wave velocity (cm/s)				*p* for trend
	900–1,269 (*n*=395)	1,270–1,493 (*n*=392)	1,494–1,821 (*n*=396)	1,822–4,128 (*n*=394)	
Age (years)	49.7±6.8	56.0±8.4	62.7±9.2	71.5±8.4	<0.0001
Heart rate (bpm)	62.9±11.9	64.9±9.9	68.6±10.0	72.8±11.9	<0.0001
Systolic blood pressure (mmHg)	107.5±17.9	121.7±15.8	135.2±15.9	150.5±19.9	<0.0001
Diastolic blood pressure (mmHg)	63.9±11.9	73.5±9.9	80.2±10.0	87.4±11.9	<0.0001
Hypertension (%)	3.2	16.9	50.2	85.5	<0.0001
Antihypertensive drugs (%)	2.5	7.4	25.7	47.5	<0.0001
β-Blocker (%)	0.2	1.4	2.6	6.0	0.0001
Calcium channel blocker (%)	1.9	6.1	20.5	38.1	<0.0001
ACE inhibitor (%)	0.0	0.5	7.3	6.9	<0.0001
ARB (%)	0.2	0.9	5.1	9.8	<0.0001
ECG abnormalities (%)	3.0	8.4	10.3	30.9	<0.0001
Total cholesterol (mmol/L)	5.2±1.0	5.5±0.9	5.6±0.9	5.4±1.0	0.01
HDL cholesterol (mmol/L)	1.8±0.5	1.8±0.4	1.7±0.4	1.6±0.5	0.0002
LDL cholesterol (mmol/L)	3.2±0.9	3.4±0.8	3.4±0.8	3.3±1.0	0.15
Triglyceride (mmol/L)	0.9±0.8	1.1±0.7	1.3±0.7	1.4±0.9	<0.0001
Dyslipidemia (%)	49.2	53.5	58.8	68.4	0.0001
Fasting plasma glucose (mmol/L)	5.4±1.2	5.8±1.1	6.0±1.1	6.4±1.3	<0.0001
HbA1c (%)	4.8±0.8	5.0±0.6	5.1±0.6	5.3±0.8	<0.0001
Diabetes (%)	3.1	8.6	12.4	34.3	<0.0001
BMI	21.7±4.0	22.8±4.0	23.6±4.0	24.0±4.0	<0.0001
Obesity (%)	28.4	24.6	30.5	39.6	0.0004
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.01
Serum potassium (mmol/L)	4.3±0.4	4.3±0.4	4.3±0.4	4.2±0.4	0.003
Alcohol intake (%)	22.5	29.3	31.1	29.3	0.69
Habitual smoking (%)	21.0	6.3	9.4	4.7	0.49

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.

Measurements of QTc and baPWV

Standard, resting 12-lead ECG was performed using an ECG device (FCP-4266; Fukuda Denshi, Tokyo, Japan) in the supine position in the morning. Heart rate (bpm) and QT interval duration (ms) were determined automatically using the PI-10 ECG Analysis Program (Fukuda Denshi). The program calculated the QT interval duration from the beginning of QRS to the end of the T wave. The QT interval duration was corrected for heart rate by calculating QTc according to Bazett's equation (*18*).

$$QTc = QT \text{ interval duration [ms]}/(60/\text{heart rate})^{1/2}$$

The baPWV was measured in the supine position after at least 5 min of rest using a volume-plethysmographic apparatus (Form PWV/ABI; Colin, Komaki, Japan), as described previously (*19*). Briefly, cuffs to measure baPWV were wrapped on both brachia and ankles. PWV at the brachia and ankles were recorded using a semiconductor pressure sensor. Volume waveforms were stored with automatic gain analysis and quality adjustment. BaPWV was automatically calculated according to the following equation: $baPWV = (L_a - L_b)/T$, with L_a being the distance from the heart to each ankle, L_b the distance from the heart to the right upper arm, and T the time delay from the right brachial waveform to each ankle waveform.

All clinical examinations including 12-lead ECG, measurement of baPWV and blood test were conducted on the same day.

Relevant Factors

At baseline examination, a self-administrated questionnaire concerning current drug use including antihypertensive agents (*e.g.*, β-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker), smoking, and alcohol intake was completed in advance by each participant and was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. Blood pressure was measured three times

after the subject had rested for at least 5 min using a semiautomatic device (BP203RVIII; Colin) based on the cuff-oscillometric principle with the subject in the sitting position. The mean of the three measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or current use of antihypertensive agents. ECG abnormalities were defined as Q wave (Minnesota codes, 1–1, 2, 3), left ventricular hypertrophy (3–1) or ST depression (4–1, 2, 3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kg divided by height in m squared. Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids, plasma glucose levels, serum calcium, and potassium. Serum total cholesterol, triglycerides, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Hemoglobin A1c levels were measured by high-performance liquid chromatography. Dyslipidemia was defined as total cholesterol ≥5.68 mmol/L, LDL-cholesterol ≥4.13 mmol/L, HDL-cholesterol <1.03 mmol/L, triglycerides ≥1.69 mmol/L, or current use of lipid-lowering agents. Diabetes was defined according to the criteria recommended by the American Diabetes Association (*20*), in addition to a medical history of diabetes. Obesity was defined as BMI ≥25.0 kg/m^2.

Statistical Analysis

The age-adjusted frequencies of relevant factors in quartile groups defined by baPWV were calculated by means of the direct method using the total study population as a standard and were compared using age-adjusted logistic regression models. The age-adjusted mean values of QTc and relevant factors in quartile groups defined by baPWV were calculated using covariance analysis and compared using multiple regression models. Multivariate-adjusted mean values of QTc in the four baPWV groups were estimated using multiple regression models including age, gender, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium levels, alcohol intake, and habitual smoking. Comparisons of the relationships of baPWV with QTc among subgroups were carried out by adding an interaction term to the statistical models. p values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS program package (SAS Institute, Cary, USA).

Ethical Considerations

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

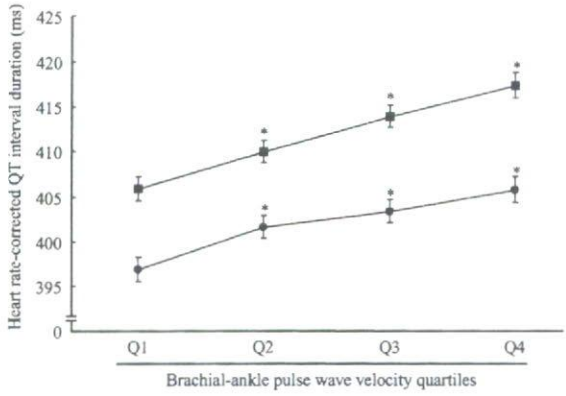

Fig. 1. *Age-adjusted mean values of heart rate–corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels for men (solid circles) and women (solid boxes). For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater. The centers of the circles or boxes are placed at the estimates of mean values. Vertical lines represent SEM for mean values. *$p<0.01$ vs. the lowest quartile group. $p<0.0001$ for trend in both men and women.*

Results

The mean value of QTc was 401.7 ms (SD, 21.5; range, 328.0–494.0) for men and 411.7 ms for women (SD, 23.3; range, 295.0–554.0). Baseline characteristics of male and female participants according to quartile groups defined by baPWV are shown in Tables 1 and 2, respectively. For men, the quartile groups were 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; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s. The subjects with higher baPWV levels were significantly older. The frequencies of hypertension, dyslipidemia, diabetes, obesity, and alcohol intake increased with rising baPWV levels, while an inverse association was observed for the frequency of habitual smoking.

Figure 1 shows the age-adjusted mean values of QTc according to quartiles of the baPWV levels by sex. The age-adjusted mean values of QTc linearly increased with rising baPWV levels for men and women: for men, 396.7, 401.4, 403.2, and 405.6 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend); for women, 405.7, 409.9, 413.8, and 417.4 ms for the 1st to 4th quartile groups, respectively ($p<0.0001$ for trend). When the Friedrich formula was used for estimation of QTc, similar associations were observed between baPWV and QTc in both men and women