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# Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population

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ABSTRACT

*Background:* High C-reactive protein (CRP) levels have been reported to be associated with an increased risk of atherosclerotic cardiovascular events. The relationship of CRP levels to the risk of cerebrovascular events in the Japanese population, which has a lower prevalence of coronary artery disease and a lower CRP level than Western populations, has not been fully clarified. The present study examined the predictive value of serum high sensitivity CRP (hs-CRP) levels for future cerebrovascular events and mortality in the general Japanese population.
*Methods:* The subjects for this community-based, prospective cohort study were recruited from the general population ($n$ = 7901, male only, mean age = 64.0 years). Serum hs-CRP levels and cardiovascular risk factors were determined at baseline. The mean follow-up period was 2.7 years. After excluding subjects with a cardiovascular history, the relationships between hs-CRP levels and cerebrovascular events and mortality were assessed.
*Results:* During follow-up, 130 participants had a first stroke (95 ischemic strokes), and 161 participants died. The hs-CRP tertile level was a significant predictor for a first ischemic stroke (3rd tertile, HR = 1.77: 95% CI, 1.04–3.03, compared with the 1st tertile), after adjustment for age and classical cardiovascular risk factors. Similar trends were observed for the prediction of all-cause mortality (3rd tertile, HR = 2.26: 95% CI, 1.49–3.42, compared with the 1st tertile).
*Conclusion:* CRP levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population, independently from traditional cardiovascular risk factors.


## 1. Introduction

The degree of systemic inflammation that is represented by elevated high sensitivity C-reactive protein (hs-CRP) levels has been associated with an increased risk of cardiovascular events in studies conducted in the United States and Europe [1–3]. In the prospective Physicians' Health Study (PHS), elevated hs-CRP levels were associated with an approximately twofold increase in the risk of stroke [1].

We previously reported that, in apparently healthy males living in Japan, hs-CRP levels were closely associated with atherosclerotic changes as measured by carotid plaque formation [4]. Thus, the extent of inflammation may reflect the propensity of atherosclerotic lesions to precipitate clinical vascular events. However, the serum hs-CRP levels of the general Japanese population have been reported to be lower than those of other ethnic groups [5,6]. One must clarify whether associations between a future risk of cerebrovascular diseases and elevated hs-CRP levels also exist in a population that has a relatively lower hs-CRP level. Only one study has reported the association between hs-CRP and ischemic stroke in a rural area of Japan [7]. Therefore, we evaluated the ability of hs-CRP levels to predict future cerebrovascular events and mortality in a larger cohort of the general Japanese population.

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## 2. Methods

### 2.1. Study subjects

The study subjects were recruited from the community-dwelling population living in the Ninohe, Kuji, and Miyako districts of Iwate in northern Japan (the Iwate-Kenpoku Cohort study). This study was conducted as part of a government-sponsored, multiphasic health checkup program aimed at the general population. Between April 2002 and January 2005, invitations to participate in this health checkup program were issued by government offices in 17 rural municipalities located in these districts; 26,469 individuals (9161 males) took part in the program and agreed to join the present study. Of these, 25,925 subjects (8957 males) had hs-CRP measurements. Subjects aged over 80 years (280 males) and those under 40 years (300 males), as well as those with a history of cardiovascular disease or stroke (527 males), were excluded. Thus, the data of 7901 males (mean age, 64.0 ± 9.7 years) were analyzed. Baseline clinical examinations included a standard 12-lead electrocardiogram, and a self-reported questionnaire was administered to document subjects' medical history and lifestyle. Hospital inpatients, persons who could not walk independently, and persons with recent inflammatory conditions, such as major trauma, surgery, or obvious acute infectious disease, were not included in the present study.

The study was approved by our institutional ethics committee, and all of the participants provided their written informed consent.

### 2.2. Risk factor definitions

The presence of baseline cardiovascular risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking, was determined. Hypertension was defined as at least one of: systolic blood pressure ≥140 mmHg; a diastolic blood pressure ≥90 mmHg; or current antihypertensive therapy. Diabetes mellitus was defined as a history of a random blood glucose level ≥200 mg/dL or an HbA1c level ≥6.5% or current anti-diabetic therapy. Dyslipidemia was defined as a total cholesterol level ≥240 mg/dL or high density lipoprotein cholesterol level <40 mg/dL or current cholesterol-lowering therapy. Obesity was defined as a body mass index ≥25.0 kg/m$^2$. The estimated glomerular filtration rate (eGFR) was calculated using the modified equation of the Modification of Diet in Renal Disease (MDRD) study [8].

An electrocardiogram was not done in 225 males (2.8%). Body height or body weight was missing in 10 males, and blood pressure data were missing in 2 males. These participants were considered to have no risk factors such as atrial fibrillation, obesity, or hypertension if they had no history of atrial fibrillation or hypertension.

### 2.3. Blood samples and hs-CRP measurement

Blood samples were collected from an antecubital vein. The samples were collected into vacuum tubes containing EDTA or a serum separator gel (CRP, lipids). After sampling, tubes were stored immediately in an icebox and centrifuged at 1500 × $g$ for 10 min within 8 h of collection. Aliquots of serum were stored at −20 °C, and routine hematology and biochemistry tests, including hs-CRP, were done within a few days after blood sampling. hs-CRP levels were determined using a highly sensitive immunonephelometric method with a coefficient of variation <5% (N Latex CRP, Dade Behring). The detection limit of CRP assay is 0.1 mg/L, and cases with levels below the limit of detection were considered as 0.1 mg/L.

### 2.4. Outcome measures

In this cohort study, the primary endpoint was all-cause death, as well as any non-fatal cardiovascular events, such as myocardial infarction, cerebral infarction, or other strokes. The dates of death and move-out were confirmed by the investigators reviewing population-register sheets in each local government. Persons who were known to be alive at the end of follow-up and those who had moved away from the study area were treated as censored cases.

Stroke events were identified by accessing the Iwate prefecture stroke registration program, which included the entire area where the subjects lived; details of this registry have been described previously [9]. Since 1991, the stroke registration program has been coordinated by the Iwate prefecture government and the Iwate Medical Association; the medical records of all medical facilities within the survey area are verified to ensure complete capture of all data. Incidents of acute myocardial infarction were identified by accessing data from the Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. The registration of acute myocardial infarction and sudden death was based on the criteria of the MONICA study [10]. To verify the accuracy of the data, a physician or trained research nurse visited and checked the medical records of the referral hospitals.

Females were excluded from the analysis due to a low incidence of ischemic stroke events (59 events in 15,457 females; 0.4%). For the same reason, coronary heart disease events (non-fatal myocardial infarction, 34 events in 7901 males; 0.4%) were also not analyzed.

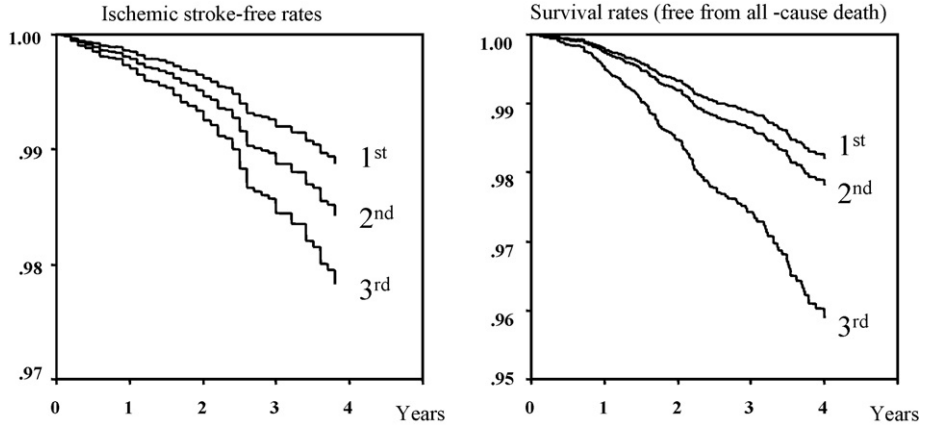


**Fig. 1.** Cumulative ischemic stroke-free rates and survival rates by age-adjusted Cox regression model for hs-CRP tertiles.

**Table 1**
Baseline clinical characteristics of all subjects with and without endpoints

| | Ischemic stroke | | | All-cause death | | |
|---|---|---|---|---|---|---|
| | (−) | (+) | *p* | (−) | (+) | *p* |
| No. of subjects | 7806 | 95 | | 7740 | 161 | |
| Age (years) | 63.9 ± 9.7 | 69.6 ± 7.2 | <0.001 | 63.9 ± 9.7 | 69.8 ± 7.8 | <0.001 |
| Body mass index (kg/m$^2$) | 23.9 ± 2.9 | 23.6 ± 3.0 | 0.20 | 24.0 ± 2.9 | 22.9 ± 3.0 | <0.001 |
| Systolic blood pressure (mmHg) | 131 ± 19 | 139 ± 20 | <0.001 | 131 ± 19 | 132 ± 20 | 0.31 |
| Diastolic blood pressure (mmHg) | 79 ± 11 | 80 ± 11 | 0.31 | 79 ± 11 | 76 ± 10 | 0.006 |
| Hemoglobin A1c (%) | 5.15 ± 0.74 | 5.28 ± 0.83 | 0.09 | 5.15 ± 0.74 | 5.30 ± 0.98 | 0.052 |
| Serum creatinine (mg/dL) | 0.82 ± 0.20 | 0.85 ± 0.16 | 0.15 | 0.82 ± 0.19 | 0.88 ± 0.42 | 0.18 |
| eGFR (mL/min/1.73 m$^2$) | 73.4 ± 15.1 | 69.2 ± 13.5 | 0.006 | 73.4 ± 15.0 | 70.2 ± 18.0 | 0.004 |
| Uric acid (mg/dL) | 5.73 ± 1.35 | 5.45 ± 1.51 | 0.038 | 5.72 ± 1.35 | 5.95 ± 1.59 | 0.16 |
| Total cholesterol (mg/dL) | 191 ± 32 | 188 ± 35 | 0.15 | 192 ± 32 | 181 ± 35 | 0.001 |
| Triglyceride (mg/dL) | 126 ± 84 | 123 ± 85 | 0.41 | 126 ± 84 | 121 ± 81 | 0.39 |
| LDL-cholesterol (mg/dL) | 114 ± 29 | 112 ± 31 | 0.25 | 114 ± 29 | 107 ± 32 | 0.023 |
| HDL-cholesterol (mg/dL) | 56 ± 15 | 56 ± 16 | 0.90 | 56 ± 15 | 53 ± 17 | 0.002 |
| hs-CRP (mg/L) | 0.54 | 0.80 | <0.001 | 0.55 | 1.07 | <0.001 |
| Hypertension (%) | 45.6 | 67.4 | <0.001 | 45.7 | 54.0 | 0.038 |
| Diabetes mellitus (%) | 7.7 | 11.6 | 0.17 | 7.6 | 14.3 | 0.004 |
| Dyslipidemia (%) | 21.6 | 18.9 | 0.61 | 21.4 | 26.1 | 0.17 |
| Obesity (%) | 33.3 | 33.7 | 0.91 | 33.5 | 26.1 | 0.052 |
| Atrial fibrillation (%) | 2.6 | 15.8 | <0.001 | 2.7 | 6.2 | 0.013 |
| Current/past smoking (%) | 62.2 | 75.8 | 0.007 | 62.2 | 68.9 | 0.085 |

hs-CRP, high sensitivity C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; eGFR: estimated glomerular filtration rate.
Log-transformed values were used for comparisons of CRP levels.
Data are shown as mean ± S.D. hs-CRP are shown as geometric mean.

### 2.5. Statistical analysis

The cumulative survival curves (free of ischemic stroke or free of all-cause death) by hs-CRP tertile levels were determined according to the age-adjusted Cox model (Fig. 1). The proportionality assumptions of the hazard by hs-CRP tertile were verified by log minus log curves. To determine the relative risks for each hs-CRP tertile level, multivariate Cox proportional hazard models were used. Age and known cardiovascular risk factors were used, and age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking, and presence of diabetes were forced into the multivariate adjusted model. One rural community ($n = 728$) was excluded from multivariate analysis because of missing data for serum uric acid, and cases having other missing data as random phenomena were also excluded. This multivariate analysis was finally performed for 7127 subjects. The results are expressed as the hazard ratio (HR) and the corresponding 95% confidence interval (CI). The analyses were performed using the SPSS statistical package, version 11.0.

## 3. Results

The mean follow-up period was 2.7 years. During follow-up, 130 subjects (1.6%) had a first stroke. Of these, 95 (1.2%) had an ischemic stroke; 161 (2.0%) died due to any cause; and 34 (0.4%) had a new onset, non-fatal myocardial infarction (MI). All of the non-ischemic strokes were the result of intracerebral or subarachnoid hemorrhages.

Baseline characteristics of the participants with and without ischemic stroke or all-cause death are shown in Table 1. Age, systolic and diastolic blood pressures, serum creatinine level, the prevalence of hypertension, atrial fibrillation, and smoking were higher in those with ischemic stroke than in those without. On the other hand, eGFR was lower in those with ischemic stroke than in those without. Similar results were obtained with respect to all-cause death. Some paradoxical relationships were found with respect to the uric acid level in participants with ischemic stroke, and the total cholesterol level and LDL level in those with all-cause death (Table 1).

The median serum hs-CRP level was 0.5 mg/L (95 percentile range: 0.1–4.3 mg/L) in males. This median hs-CRP level was lower than the levels reported in other populations in which hs-CRP levels were measured using the same assay methodology [1–3]. A total of 917 participants showed CRP levels ≤0.1 mg/L. Overall tertile ranges for the hs-CRP levels were: 1st, 0.1–0.3; 2nd, 0.4–0.7; and 3rd, ≥0.8 mg/L. Participants showing CRP > 10.0 mg/L comprised 1.7% of the study population. However, presence of acute infectious condition cannot be judged by CRP level alone, so making a cut-off level for infection is not possible. We therefore ventured to perform analyses without any exclusion criteria for high CRP level.

**Table 2**
Hazard ratios for first ischemic stroke and all-cause death by hs-CRP tertile levels

| | hs-CRP tertile | Incidence of events/no. of subjects, *n* (%) | Age adjusted hazard ratios (95% CI) | *p* | Multivariate adjusted hazard ratios (95% CI)[a] | *p* |
|---|---|---|---|---|---|---|
| Ischemic stroke | 1 | 22/2922 (0.75) | 1.00 (reference) | | 1.00 (reference) | |
| | 2 | 28/2296 (1.22) | 1.41 (0.80–2.48) | 0.24 | 1.30 (0.72–2.33) | 0.39 |
| | 3 | 45/2683 (1.68) | 1.95 (1.17–3.25) | 0.010 | 1.77 (1.04–3.03) | 0.037 |
| All-cause death | 1 | 36/2922 (1.23) | 1.00 (reference) | | 1.00 (reference) | |
| | 2 | 37/2296 (1.61) | 1.22 (0.77–1.93) | 0.40 | 1.15 (0.71–1.88) | 0.57 |
| | 3 | 88/2683 (3.28) | 2.32 (1.57–3.42) | <0.001 | 2.26 (1.49–3.42) | <0.001 |

hs-CRP, high sensitivity C-reactive protein; CI, confidence interval.
[a] Age (10-year increase), systolic blood pressure, total cholesterol, high density lipoprotein cholesterol, uric acid, estimated glomerular filtration rate, body mass index, smoking (current and past), and the presence of diabetes were forced into the Cox regression analysis model.

As shown in Fig. 1, first ischemic stroke-free survival was lower in the higher hs-CRP tertile level when adjusted for age ($p = 0.034$). Similar results were observed for all-cause death-free survival rates ($p < 0.001$). The proportionality assumptions of the hazard by hs-CRP tertiles for these outcomes were satisfied.

In the multivariate Cox regression analysis model adjusted by age, a significantly increased hazard ratio of ischemic stroke was found in the 3rd hs-CRP tertile (HR = 1.95, $p = 0.010$) compared to the 1st hs-CRP tertile. After adjustment for age (10-year increase) and other classical cardiovascular risk factors, such as systolic and diastolic blood pressures, total cholesterol, high density lipoprotein cholesterol, uric acid, eGFR, BMI, smoking (current and past), and the presence of diabetes, the estimated HRs were maintained in the 3rd hs-CRP tertiles (HR = 1.77, $p = 0.037$). The results of the analysis of all-cause death were similar (Table 2). When the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke, the statistical significance of the hs-CRP tertiles declined (3rd hs-CRP tertile, HR = 1.56, $p = 0.10$).

On the other hand, there was no significant association between the hs-CRP tertiles and strokes from any causes (trend $p = 0.19$) in the model adjusted by age and other classical cardiovascular risk factors.

## 4. Discussion

This prospective cohort study found that baseline serum hs-CRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population. It is interesting that these results were obtained in the Japanese population, which has a lower median hs-CRP level than Western populations [4,5].

The major risk factors for stroke and cardiovascular disease, such as smoking, diabetes, and hypertension, are associated with higher hs-CRP levels [11,12]. These relationships could potentially explain the associations that have been found between hs-CRP level and stroke or mortality. However, since adjustment for such risk factors did not have a large effect on the associations, the traditional risk factors cannot completely explain the relationship between the hs-CRP level and ischemic stroke events.

Carotid plaque formation is a well-established predictor for future ischemic stroke in the general population [13,14]. Our previous data showed a close association between the hs-CRP level and the severity of carotid atherosclerosis as demonstrated by plaque formation in men [6]. The present prospective results show that future stroke events were related to elevated baseline hs-CRP levels; this finding appears to substantiate our previous cross-sectional data. Although a significant association between the hs-CRP level and carotid atherosclerosis was only seen in men in our previous data, the present study could not demonstrate a gender difference for the association between hs-CRP level and the study endpoint.

Atrial fibrillation has been known to be closely related with ischemic stroke due to cardiac thromboembolism. In the present study, the presence of atrial fibrillation was the strongest predictor for ischemic stroke in the same model of multivariate Cox regression analysis with various risk factors (HR = 5.13, 95% CI; 2.82–9.35, $p < 0.001$). It is considered natural that the significance of the hs-CRP tertiles declined when the presence of atrial fibrillation was included in the multivariate adjusted model for ischemic stroke.

In the present cohort, the association between elevated hs-CRP level and stroke was only present when the analysis was limited to the ischemic stroke subtype. In the present study's subjects, all non-ischemic strokes were intracranial hemorrhages, which are known to be caused by rupture of cerebral perforating arteries or an intracranial aneurysm. These pathological conditions develop primarily due to hypertension and small artery hyalinosis [15]. The relationship between cerebral aneurysm and atherosclerosis is not considered to be very strong [16]. Few large-scale prospective cohort studies have addressed stroke subtype.

The major results of our study are completely consistent with the findings of the Hisayama Study [7]. Although the novelty of our study may be lacking, we would raise some unique minor points of difference from the findings and design of the Hisayama Study. First, the presence of atrial fibrillation reduced the predictive power of CRP for ischemic stroke in our study. Second, hs-CRP measurement at baseline was planned a priori and the assay was performed immediately, without long-term cryopreservation. Third, registration of our study population was started in 2002. Compared with the survey in 1988 of the Hisayama study, many new anti-atherosclerotic agents such as strong statins, long-acting anti-hypertensive agents and angiotensin-receptor blockers were likely to be in more frequent use in our study population. Furthermore, our study population comprised older, more obese subjects compared with those in Hisayama Study. All of these characteristics are thought to represent a closer fit with modern Japanese society and community population.

It is possible that the hospital-based follow-up used in the present study was not completely reliable for detecting clinical events. However, an attempt was made to retrieve and view all medical charts from all hospitals and clinics located in the survey area, and the study included several remote teaching hospitals and tertiary referral medical centers. Furthermore, the population of the study district has been stable, with an annual variation rate of only 0.2%. Moreover, participants who developed cerebrovascular and cardiovascular diseases or fatal events had access to only a limited number of medical institutes. Therefore, most major clinical adverse events were likely to have been captured in the present study cohort.

Elevated hs-CRP levels did not reflect the presence of imminent diseases from which stroke events or all-cause deaths had not yet occurred, since the interval between baseline hs-CRP measurement and the ischemic stroke event or death was relatively long: a mean of 1.8 years for ischemic stroke events and a mean of 1.9 years for all-cause death.

Some study limitations should be noted. The results of this study are based on one baseline hs-CRP measurement. Subjects who had recent acute inflammatory conditions, other than a mild "common cold", were not included in the study. However, the subjects were not examined to determine whether any chronic infections, including silent infections such as periodontitis, bladder cystitis, and chronic bronchitis, were present. Chronic infections have been known to have a relationship with carotid atherogenesis [17]. The present study did not assess the use of drugs that can lower hs-CRP levels, such as rennin–angiotensin system inhibitors [18,19], statins [20], and thiazolidinedione [21]. However, it was unlikely that the frequency of the use of these medications was higher in event-free participants. Although imaging was used to verify all stroke cases who visited the hospital with typical symptoms of neurological deficit, patients with events who were not hospitalized or those who were hospitalized at hospitals located outside the area could not be captured in this study design. However, this occurred very infrequently. Finally, this study tested several possible outcomes, including stroke and coronary heart disease in each gender, and then reported the significant findings. The possibility thus remains that chance findings were responsible for the present results.

In conclusion, CRP levels can predict future ischemic stroke and mortality in Japanese males from the general population, independently from traditional cardiovascular risk factors other than atrial fibrillation.

## Conflict of interest

The authors report no conflicts of interest.

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