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M.O. had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Appendix A

A.1. Members of Iwate-KENCO Study

Chairman: Akira Okayama (The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo)

Principal investigators: Akira Ogawa, Motoyuki Nakamura, YasuoTerayama, Kazuyoshi Itai, Toshiyuki Onoda, Masaki Ohsawa, Kozo Tanno, Kiyomi Sakata, Yuki Yoshida (Iwate Medical University, Morioka), Mitsumasa Tazawa (Morioka Public Health Care Center), Kazuko Kawamura (Iwate Health Service Association), Toru Kuribayashi (Iwate University, Morioka)

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2008.01.008.

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Cardiovascular risk factors in the Japanese northeastern rural population ☆

Masaki Ohsawa [a,*], Kazuyoshi Itai [a], Kozo Tanno [a], Toshiyuki Onoda [a], Akira Ogawa [b], Motoyuki Nakamura [c], Toru Kuribayashi [d], Yuki Yoshida [b], Kazuko Kawamura [e], Satoshi Sasaki [f], Kiyomi Sakata [a], Akira Okayama [g]

[a] *Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Japan*
[b] *Department of Neurosurgery, School of Medicine, Iwate Medical University, Japan*
[c] *Department of Internal Medicine II, School of Medicine, Iwate Medical University, Japan*
[d] *Department of Health and Physical Education, Faculty of Education, Iwate University, Japan*
[e] *Iwate Health Service Association, Japan*
[f] *National Institute of Health and Nutrition, Japan*
[g] *The First Institute of Health Service, Japan Anti-Tuberculosis Association, Japan*

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Abstract

Background: People living in the northeastern part of Japan have high prevalences of hypertension and stroke. The current status of cardiovascular risk factors in them should be elucidated.
Methods: The survey was carried out from 2002 to 2004 in the northeastern part of the main island of Japan. A total of 26,472 Japanese men and women were enrolled (acceptance rate: 84.5%). Sex- and age-specific prevalences of cardiovascular risk factors were determined. Mean values of predictive markers (high-sensitivity C reactive protein (hsCRP), brain natriuretic peptide (BNP) and microalbuminuria) were also determined in each group. Risk factor-related variables in non-hypertensive subjects and hypertensive subjects were compared.
Results: Proportions of subjects with hypertension, diabetes and dyslipidemia were 46.0%, 7.6%, and 30.3%, respectively, in males and 38.6%, 4.0%, and 38.5%, respectively, in females. Mean values of hsCRP and BNP were 1.41 mg/L and 26.5 pg/mL, respectively, in males and 1.01 mg/L and 23.7 pg/mL, respectively, in females. Proportions of male and female subjects with microalbuminuria were 22.0% and 23.4%, respectively. These markers become higher with advance of age. Prevalence of atrial fibrillation was 1.56%, and it increased with advance of age in both men and women. High prevalences of cardiovascular risk factors in this area were found. Hypertensive subjects who did not take anti-hypertension medication accounted for about 20% of total subjects and their blood pressure remained poorly controlled.
Conclusion: Attention should be given to cardiovascular risk factors in the Japanese northeastern rural population.

Keywords: Cardiovascular risk factors; C-reactive protein; Brain natriuretic peptide; Microalbuminuria; Atrial fibrillation; The Iwate-KENCO study

1. Introduction

People living in the northeastern part of the main island of Japan (Tohoku area) have high prevalences of hypertension and stroke compared with those in people living in other areas [1,2] and they have a large intake of salt [3]. Attention should be given to the current status of cardiovascular risk factors in people living in this area of Japan.

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* Corresponding author. Department of Hygiene and Preventive Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka 020-8505, Japan. Tel.: +81 19 651 5111x3373; fax: +81 19 623 8870.
E-mail address: masakio@iwate-med.ac.jp (M. Ohsawa).

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Fig. 1. The study area. This figure shows a map of Japan and a map of Iwate Prefecture. Iwate Prefecture is located in the northeastern part of the main island (Honshu Island) of Japan. The black area of Iwate Prefecture indicates the study area. Kenpoku means northern part of the prefecture in Japanese.

We have conducted a population-based prospective cohort study in the northeastern part of Japan. The aims of the present study were to determine the age- and sex-specific prevalences of cardiovascular diseases (CVD) and their risk factors by a cross-sectional analysis of data from the initial survey. We also compared cardiovascular risk factor-related characteristics in hypertensive subjects and non-hypertensive subjects to clarify the status of clustering risk factors in hypertensive subjects.

2. Subjects and methods

2.1. Study subjects

The "Iwate KENpoku COhort Study (Iwate-KENCO Study)" is a population-based prospective study in people living in the northeastern part of the main island of Japan (Fig. 1). The initial surveys were carried out from 2002 to 2004. Each survey was conducted from April to November. The study area is a typical rural area of Japan with a low move-out/move-in population, high proportion of people engaged in primary industry (18.4%) [4] and high proportion of elderly people (people aged 65 years or more: 26.2% of the total population). The study area consists of 17 municipalities, and the total population of the region in 2002 was 241,057. Invitations to multiphasic health screening were issued by government offices in the municipalities. A total of 31,318 people (11,003 men and 20,315 women) aged 18 years or older participated in annual health check-ups from 2002 to 2004 in the study area. Of those participants, 26,472 men and women gave written informed consent for participation in this study (acceptance rate: 84.5%). Sex- and age-specific numbers and proportions of participating subjects and acceptance rates are shown in Table 1. The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

2.2. Measurements

Measurements of blood pressure were performed by well-trained staff. Weight was measured with an automated scale (TANITA digital scale Model BWB-200). Height was measured using a digital handle scale (YAGAMI model 48525YG-200D). Blood pressure was measured twice in the sitting position using an automatic device (BP-103i IIModel 513000, Nippon Colin, Komaki, Japan) after urination and a five-minute rest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each calculated as the mean of two measurements. Body mass index (BMI) was calculated as weight (kg) divided by the square of body height (m).

Self-administered questionnaires on demographic characteristics, history of cardiovascular disease and apoplexy, drug use, alcohol consumption, smoking, and exercise habit were used to collect individual information. Details were described previously [5].

A nutrition survey was carried out in each municipality. This survey was an optional survey and was carried out at each participant's own discretion (executing rate: 72.4%). Dietary habits during the previous month were assessed using a brief

Table 1
Age- and sex-specific numbers of participants, acceptance rates, and proportions of total population in the study area

Age group	18–29	30–39	40–49	50–59	60–69	70–79	≥80	Total
Total population in the study area (*n*)	18,692	26,036	29,850	35,001	33,673	29,301	14,494	233,307
Participants of check-ups (*n*)	330	1302	3289	6449	11,038	8115	1078	31,318
Participants of the study (*n*)	266	1064	2793	5537	9376	6869	797	26,472
Acceptance rate (%)	80.6%	81.7%	84.9%	85.9%	84.9%	84.6%	73.9%	84.5%
Proportion of total population (%)	1.4%	4.1%	9.4%	15.8%	27.8%	23.4%	5.5%	11.3%
Total male population (*n*)	9326	12,940	15,019	17,113	15,081	12,475	4379	109,749
Participants of check-ups (*n*)	108	367	1005	1841	3930	3345	498	11,003
Participants of the study (*n*)	83	296	813	1520	3281	2863	385	9162
Acceptance rate (%)	76.9%	80.7%	80.9%	82.6%	83.5%	85.6%	77.3%	83.3%
Proportion of total population (%)	0.9%	2.3%	5.4%	8.9%	21.8%	22.9%	8.8%	8.3%
Total female population (*n*)	9366	13,096	14,831	17,888	18,592	16,826	10,115	123,558
Participants of check-ups (*n*)	214	935	2284	4608	7108	4770	580	20,315
Participants of the study (*n*)	180	768	1980	4017	6095	4006	412	17,310
Acceptance rate (%)	84.1%	82.1%	86.7%	87.2%	85.7%	84.0%	71.0%	85.2%
Proportion of total population (%)	1.9%	5.9%	13.4%	22.5%	32.8%	23.8%	4.1%	14.0%

Data are expressed as numbers or percentages.

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self-administered diet history questionnaire (BDHQ). This is a 4-page structured questionnaire that consists of three sections: general dietary behavior and main cooking methods, consumption frequencies and amounts of intake of 5 alcoholic beverages, and frequencies of consumption of 50 selected food and nonalcoholic beverage items. Estimates of dietary intake of 48 food and beverage items, energy and nutrients were calculated using an ad hoc computer algorithm for the BDHQ, which was mainly based on the Standard Tables of Food Composition in Japan [6]. Results of validation study for the BDHQ were previously described in detail [7].

A resting 12-lead electrocardiogram was recorded in each participant after a five-minute rest. The electrocardiographic findings were independently evaluated by a trained clinical technician and a medical doctor in Iwate Health Service Association according to the original coding system developed by Iwate Health Association. In this study, sex- and age-specific prevalences of atrial fibrillation (AF) were determined. AF was defined according to the original coding system (including paroxysmal atrial fibrillation and atrial flutter).

2.3. Biochemical analyses

Casual blood samples were drawn from antecubital veins of seated participants. The samples were transported to a laboratory (Iwate Health Service Association) and analyzed on the same day.

Total cholesterol (TC) levels were determined by an enzymatic assay, triglyceride (TG) levels were determined by an enzyme-colorimetric assay, high-density lipoprotein cholesterol (HDLC) levels and low-density lipoprotein cholesterol (LDLC) levels were determined by a direct quantitative assay, and plasma glucose levels were determined by the hexokinase ultraviolet method. All of the above biochemical data were analyzed using an automated analyzer (HITACHI 7700). Glycosylated hemoglobin (HbA_{1c}) levels were determined by high-performance liquid chromatography using an automated analyzer (TOSOH HLC-723G7 Japan). Determinations of TC levels and HDLC levels were performed under the quality control program of the Center for Disease Control in the United States [5].

Serum levels of high-sensitivity C-reactive protein (hsCRP) were determined by the latex-enhanced immunonephelometric method (Dade Behring Diagnostics, Germany) with a threshold of 0.1 mg/L. In this estimation, hsCRP values under the minimum detectable level were regarded as being 0.1 mg/L. Plasma brain natriuretic peptide (BNP) levels were measured by a direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi and Co., Ltd., Japan). Plasma BNP assays were performed for 65.6% of the subjects in the study. The method for measuring plasma BNP levels was previously described in detail [8].

Urine albumin was assessed quantitatively by an immunonephelometric method (N-antiserum albumin, Dade Behring) and urine creatinine was measured quantitatively by an enzymatic colorimetric test [9]. The urine albumin–creatinine ratio (UACR) was used since the accuracy of the ratio in comparison to a 24-hour urine sample has been demonstrated in previous studies [10,11].

2.4. Classification and definition

To examine to what extents traditional risk factors, dietary intake of nutrients and new predictive markers (hsCRP, BNP, and urine albumin) are associated with age in a cross-sectional analysis, we divided the participants into age-specific groups (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80 years or older) for both sexes. Hypertension was defined as SBP being 140 mmHg or higher, DBP being 90 mmHg or higher, use of antihypertensive agents or a combination of these. Diabetes mellitus (DM) was defined as plasma glucose level being 200 mg/dL or higher, plasma HbA_1c level being 6.5% or higher, use of anti-diabetes agents or a combination of these. Dyslipidemia was defined as serum TC level being 220 mg/dL or higher, serum HDLC level being less than 40 mg/dL, use of anti-hyperlipidemia agents or a combination of these. In current drinkers, regular alcohol drinking was defined as drinking five days or more per week and occasional drinking was defined as drinking less than five days per week. In non-current drinkers, subjects were divided into past drinkers and non-drinkers. Regular exercise was defined as doing exercise for at least 60 min eight days or more per month, and exercise habit was defined as doing exercise for at least 60 min per month. Overweight was defined as BMI being 25 kg/m^2 or more and obesity was defined as BMI being 30 kg/m^2 or more.

In most previous studies, subjects with high CRP level (10 mg/L or higher) were excluded to avoid analysis of data from subjects who had developed apparent inflammatory disease [12]. Both mean hsCRP level in all subjects and that in subjects after excluding subjects with hsCRP levels greater than 10 mg/L are shown in this study. We defined high BNP level as 50 pg/mL or more according to our previous study [8]. Macroalbuminuria was defined as UACR being 300 mg/g or more, and microalbuminuria was defined as UACR being 30 mg/g or more and less than 300 mg/g. To estimate the proportion of participants with microalbuminuria, subjects with macroalbuminuria were excluded.

2.5. Statistical analysis

Prevalences of risk factors were determined in each age- and sex-specific group. Mean values (standard deviations) of risk factor-related variables were also determined in each group. Linear trend tests were used to examine the association between age and each variable after adjusting for other traditional risk factors (SBP, BMI, TC, HDLC, HbA_{1c}, and current smoking status). Comparisons of hsCRP levels, BNP levels, and urinary albumin levels in men and women were performed using the Mann–Whitney U test. The chi-square test was used to compare the proportions of subjects between the groups. Sex difference in the prevalence of AF was tested after direct age adjustment.

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Age-adjusted SBP, TC, HDLC, LDLC, and HbA_{1c} were compared between the three groups according to presence of hypertension (non-hypertensive subjects, hypertensive subjects with medication, hypertensive subjects without medication) using analysis of covariance (ANCOVA). Prevalences of overweight, obesity, DM, and dyslipidemia were also compared between the three groups using age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) by logistic regression analysis.

All p values were based on two-sided tests, and p values less than 0.05 were considered to be statistically significant. The Statistical Package for Social Sciences (SPSS Japan Inc., version 14.0, Tokyo) was used for the analyses.

3. Results

Table 2 shows age- and sex-specific characteristics of participants with regard to demographic, biochemical and comorbid conditions. SBP and HbA_{1c} levels were higher with advance of age in both sexes (trend $p<0.01$). Prevalences of hypertension and DM were higher with advance of age in both sexes (trend $p<0.01$). The proportions of subjects with hypertension were more than 50% in males aged 50 years or older and in females aged 60 years or older. The proportions of subjects with dyslipidemia were about 30% in middle-aged males and about 40% in females aged 50 years or older. Prevalences of myocardial infarction and stroke were very low in both sexes.

Table 3 shows age- and sex-specific proportions of subjects with a smoking habit, drinking habit, and exercise habit. The proportion of current smokers in males aged 49 years or younger was more than 50%. The proportion of current smokers was very low in the female subjects, but it exceeded 15% in females aged 39 years or younger. The proportion of regular drinkers in middle-aged male subjects

Table 2
Age- and sex-specific prevalences of cardiovascular diseases and mean levels of their risk factor-related variables

Age group Men (n)		18–29	30–39	40–49	50–59	60–69	70–79	≥80	Total	Trend	Sex difference
Men (n)		86	214	813	1520	3281	2863	385	9162		
BMI	(kg/m^2)	22.4 (3.8)	24.2 (3.5)	24.1 (3.1)	24.3 (3.0)	24.1 (2.9)	23.6 (3.0)	23.0 (2.9)	23.9 (3.0)		‡
BMI≥25		25.6%	36.0%	34.9%	39.1%	36.3%	30.9%	21.3%	34.2%		
BMI≥30		5.8%	5.6%	4.2%	4.2%	2.8%	2.2%	0.8%	3.0%		
SBP	(mmHg)	114.2 (11.6)	119.9 (15.7)	122.1 (16.4)	127.5 (19.0)	131.9 (19.7)	133.8 (19.5)	136.9 (20.7)	130.7 (19.6)	†	‡
TC	(mg/dL)	171.7 (35.6)	192.3 (36.7)	197.1 (36.2)	195.8 (32.2)	191.4 (32.0)	188.0 (31.3)	184.2 (30.4)	191.1 (32.5)		
TG	(mg/dL)	122.4 (85.6)	144.0 (97.1)	154.4 (106.6)	135.7 (93.5)	124.6 (83.3)	113.1 (68.8)	104.3 (54.1)	125.1 (83.6)		
HDLC	(mg/dL)	53.7 (13.4)	55.3 (13.9)	56.4 (15.6)	56.8 (15.5)	56.1 (15.4)	55.5 (15.2)	54.3 (13.4)	56.0 (15.2)		
LDLC	(mg/dL)	102.1 (33.5)	116.7 (32.7)	117.3 (32.5)	116.3 (29.4)	113.4 (29.4)	111.9 (27.6)	109.7 (27.5)	113.6 (29.3)		
PG	(mg/dL)	92.8 (14.6)	99.0 (30.1)	107.8 (35.9)	113.4 (35.4)	115.8 (34.6)	116.6 (36.7)	117.6 (34.5)	114.4 (35.5)	†	‡
HbA_{1C}	(%)	4.68 (0.30)	4.81 (0.49)	4.99 (0.81)	5.12 (0.74)	5.18 (0.73)	5.20 (0.74)	5.17 (0.63)	5.14 (0.74)	†	
MI		0.0%	0.0%	0.0%	0.1%	0.8%	1.4%	1.3%	0.8%		‡
Stroke		0.0%	0.0%	0.1%	0.3%	0.4%	0.7%	0.3%	0.4%		‡
DM		0.0%	0.9%	3.8%	6.7%	8.4%	9.1%	7.8%	7.6%	†	‡
HTN		0.0%	10.7%	21.4%	35.4%	50.0%	55.9%	61.6%	46.0%	†	‡
DL		22.1%	30.4%	33.0%	33.3%	30.1%	29.0%	27.0%	30.3%		
Women (n)		180	620	1980	4017	6095	4006	412	17,310		
BMI	(kg/m^2)	21.7 (4.3)	22.5 (3.7)	23.4 (3.6)	24.0 (3.4)	24.3 (3.4)	24.3 (3.5)	24.0 (3.5)	24.0 (3.5)		
BMI ≥25	(%)	13.9%	22.1%	28.0%	35.1%	39.9%	40.4%	34.8%	36.5%		
BMI ≥30	(%)	6.7%	4.8%	5.3%	5.5%	5.5%	6.0%	3.5%	5.5%		
SBP	(mmHg)	102.1 (11.1)	107.5 (14.1)	115.1 (16.8)	121.9 (19.3)	127.9 (19.4)	132.3 (19.6)	135.3 (20.7)	125.2 (20.1)	†	
TC	(mg/dL)	167.8 (29.0)	176.5 (30.0)	192.3 (31.6)	209.6 (32.7)	209.4 (30.8)	206.3 (30.3)	201.2 (33.1)	205.0 (32.4)		
TG	(mg/dL)	75.7 (69.3)	89.3 (62.5)	98.2 (77.4)	112.1 (68.3)	117.5 (64.6)	117.5 (62.7)	113.2 (54.5)	112.5 (66.9)		
HDLC	(mg/dL)	62.7 (14.6)	63.3 (14.1)	63.6 (14.5)	63.0 (14.4)	60.4 (14.2)	59.6 (14.3)	58.6 (13.4)	61.2 (14.4)		
LDLC	(mg/dL)	95.1 (26.7)	100.8 (26.1)	113.1 (28.2)	126.1 (29.7)	127.0 (27.8)	124.8 (27.0)	121.5 (28.1)	123.3 (28.9)		
PG	(mg/dL)	90.7 (11.9)	94.1 (14.3)	100.7 (22.2)	104.4 (25.0)	108.0 (26.9)	110.9 (28.3)	116.6 (33.6)	106.5 (26.5)	†	
HbA_{1C}	(%)	4.65 (0.28)	4.75 (0.41)	4.88 (0.52)	5.08 (0.64)	5.16 (0.66)	5.21 (0.62)	5.23 (0.72)	5.10 (0.63)	†	
MI		0.0%	0.0%	0.0%	0.0%	0.2%	0.6%	1.7%	0.3%		
Stroke		0.0%	0.2%	0.2%	0.2%	0.3%	0.2%	0.7%	0.2%		
DM		0.0%	0.2%	1.8%	3.0%	4.3%	5.9%	7.5%	4.0%	†	
HTN		0.6%	4.2%	12.3%	28.5%	43.5%	58.7%	63.8%	38.6%	†	
DL		8.9%	9.4%	20.9%	41.0%	44.2%	42.2%	35.9%	38.5%		

Data are expressed as means (standard deviations) or percentages. †, $p<0.05$ by linear trend test. ‡ means significantly higher than that in the other sex, and p value (<0.05) was estimated by Student's t-test or the chi square test. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; PG, casual plasma glucose; HbA_{1c}, percentage of glycosylated hemoglobin; MI, myocardial infarction; DM, diabetes mellitus; HTN, hypertension; DL, dyslipidemia.

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Table 3
Age- and sex-specific cardiovascular risk factors: proportions of subjects with smoking, alcohol drinking, and exercise habits

Age group	18–29	30–39	40–49	50–59	60–69	70–79	≥80	Total	Trend	Sex difference
Men (*n*)	86	214	813	1520	3281	2863	385	9162		
Smoking status										
Current	57.0%	58.9%	55.0%	41.4%	27.6%	21.9%	16.6%	31.1%	†	‡
Ex-smoker	4.7%	14.0%	23.0%	25.5%	31.0%	38.0%	37.1%	31.2%	†	‡
Non-smoker	38.4%	27.1%	22.0%	33.2%	41.5%	40.1%	46.2%	37.8%		
Drinking habit										
≥5 days/week	26.7%	51.4%	55.2%	54.9%	46.1%	38.1%	29.4%	45.1%		‡
<5 days/week	32.6%	26.6%	23.1%	22.8%	24.0%	20.7%	17.7%	22.6%		‡
Non-drinker	39.5%	17.8%	19.4%	18.0%	21.1%	28.3%	40.0%	23.6%		
Ex-drinker	1.2%	4.2%	2.2%	4.3%	8.9%	12.9%	13.0%	8.8%		‡
Exercise habit										
≥60 min*8 times/month	17.4%	8.4%	5.3%	9.8%	20.0%	21.2%	22.9%	17.2%		‡
≥60 min/month	37.2%	29.9%	25.7%	30.2%	40.6%	42.9%	41.6%	38.0%		
Women (*n*)	180	620	1980	4017	6095	4006	412	17,310		
Smoking status										
Current	21.7%	15.2%	7.0%	3.4%	1.1%	0.7%	0.0%	2.9%	†	
Ex-smoker	11.7%	9.4%	4.4%	1.2%	0.6%	0.5%	0.5%	1.6%	†	
Non-smoker	66.7%	75.5%	88.6%	95.4%	98.4%	98.8%	99.5%	95.5%		
Drinking habit										
≥5 days/week	7.8%	11.9%	9.8%	4.5%	3.0%	1.9%	2.9%	4.2%	†	
<5 days/week	34.4%	36.5%	27.4%	19.1%	11.4%	6.7%	4.4%	14.9%	†	
Non-drinker	48.9%	48.1%	60.9%	74.4%	84.5%	90.4%	91.3%	79.3%		
Ex-drinker	8.9%	3.5%	1.9%	2.0%	1.1%	0.9%	1.5%	1.5%		
Exercise habit										
≥60 min*8 times/month	11.1%	6.3%	7.1%	10.8%	12.1%	10.2%	11.4%	10.6%		
≥60 min/month	26.1%	26.1%	27.1%	33.9%	35.8%	33.0%	29.6%	33.1%		

Proportions are expressed as percentages.
†and ‡ are explained in Table 2.

was more than 50%. The proportions of subjects doing regular exercise were 17.2% in males and 10.6% in females. Among persons aged 30 to 59 years, the proportion of subjects doing regular exercise was less than 10% in both sexes.

Table 4 shows age- and sex-specific mean levels of daily dietary intake of nutrients. The most notable characteristic in this study population is a very high level of dietary intake of salt in middle-aged and elderly people. Dietary intake of salt was about 13 g/day in males aged 39 years or younger and became higher with advance of age, exceeding 16 g/day in males aged 60 years or older. Dietary intake of salt was about 10 g/day in females aged 39 years or younger. It also became higher with advance of age and exceeded 13 g/day in females aged 60 years or older.

Mean dietary intake of carbohydrate (percent of total energy) was about 55% in both sexes. Mean dietary intake of fat was about 23% in males and it was 25% in females. Dietary intake of saturated fatty acid was about 6% in males and it was about 7% in females. Dietary intake of monounsaturated fatty acid was about 8% in males and it was about 9% in females. Ratios of n-6PUFA to n-3PUFA in the diet were 3.3 in males and 3.4 in females. The ratio exceeded 4.0 in subjects aged 39 years or younger in both sexes, but the ratio became lower with advance of age (trend $p<0.05$).

Table 5 shows age- and sex-specific mean levels of hsCRP, BNP, urinary albumin , and UACR. Mean hsCRP levels were 0.92 mg/L in males and 0.75 mg/L in females after excluding subjects with apparent inflammation. Levels of hsCRP were positively associated with age in both sexes (trend $p<0.01$). Levels of hsCRP in males were higher than those in females ($p<0.05$).

BNP levels were positively associated with age in both sexes (trend $p<0.01$). Crude BNP levels were higher in men than women in total subjects ($p<0.01$), but they were lower in male subjects aged less than 60 years than in females aged less than 60 years ($p<0.01$). Our data showed that about 16% of total subjects aged 60–69 years, 20% of total subjects aged 70–79 years and more than 40% of total subjects aged 80 years or more had BNP levels of 50 pg/mL or higher in both sexes.

Mean crude urinary albumin concentration and mean UACR in the male subjects were 45.6 mg/L and 54.7 mg/g, respectively, and those in females were 25.2 mg/L and 39.5 mg/g, respectively. Macroalbuminuria was seen in 3.1% of total male subjects and in 1.6% of female subjects. After excluding subjects with macroalbuminuria, proportions of subjects with microalbumimnuria were less than 10% in the 18 to 39 years age group and 10–20% in the 40 to 59 years age group in both sexes. Both prevalence of microalbuminuria and

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Table 4
Age- and sex-specific mean levels of daily dietary intake of nutrients

Age group	18–29	30–39	40–49	50–59	60–69	70–79	≥80	Total	Trend	Sex difference
Men (*n*)	69	182	679	1255	2550	1399	175	6309		
Total energy kcal/day	2500±783	2436±803	2585±802	2611±823	2480±786	2369±755	2397±877	2489±796		‡
CHD g/day (%)	358.2 (57.4%)	342.8 (56.3%)	363.3 (56.5%)	361.4 (55.5%)	339.8 (55.1%)	321.9 (54.7%)	319.3 (53.9%)	342.4 (55.3%)		
Protein g/day (%)	83.6 (13.4%)	81.2 (13.5%)	85.9 (13.4%)	94.2 (14.5%)	97.3 (15.7%)	97.8 (16.5%)	101.8 (16.9%)	95.1 (15.3%)		
Fat g/day (%)	63.8 (23.0%)	58.6 (21.9%)	58.0 (20.3%)	62.4 (21.4%)	63.3 (22.8%)	64.9 (24.3%)	71.3 (26.2%)	63.0 (22.6%)		
SFA	16.6 (6.0%)	15.5 (5.8%)	14.5 (5.1%)	15.7 (5.4%)	15.8 (5.7%)	16.1 (6.1%)	17.6 (6.5%)	15.7 (5.7%)		
MUFA	22.1 (8.0%)	20.3 (7.6%)	19.9 (7.0%)	21.1 (7.2%)	21.2 (7.6%)	21.7 (8.1%)	24.2 (8.8%)	21.2 (7.6%)		
PUFA	16.9 (6.1%)	15.2 (5.7%)	15.8 (5.5%)	16.8 (5.8%)	17.2 (6.2%)	17.7 (6.6%)	19.4 (7.1%)	17.1 (6.1%)		
n-6PUFA	14.0 (5.1%)	12.2 (4.6%)	12.4 (4.4%)	12.7 (4.4%)	12.6 (4.5%)	12.9 (4.8%)	14.4 (5.3%)	12.7 (4.6%)		
n-3PUFA	3.5 (1.3%)	3.2 (1.2%)	3.5 (1.2%)	4.0 (1.4%)	4.2 (1.5%)	4.4 (1.6%)	4.7 (1.7%)	4.1 (1.5%)		
αlinolenic acid	2.3 (0.8%)	2.0 (0.7%)	2.1 (0.7%)	2.1 (0.7%)	2.1 (0.8%)	2.2 (0.8%)	2.5 (0.9%)	2.2 (0.8%)		
EPA+DHA	1.2 (0.4%)	1.2 (0.5%)	1.4 (0.5%)	1.8 (0.6%)	2.1 (0.7%)	2.2 (0.8%)	2.2 (0.8%)	1.9 (0.7%)	†	
n6/n3 ratio	4.2±1.0	4.0±0.8	3.8±0.9	3.4±0.9	3.2±0.9	3.2±1.0	3.3±1.0	3.3±1.0	†	
Cholesterol mg/day	353±148	355±152	375±181	416±210	431±220	443±232	480±271	423±218		‡
Salt g/day	13.8±5.2	13.3±4.6	14.4±4.8	15.8±5.5	16.6±5.4	16.9±5.6	17.5±6.4	16.2±5.5	†	
Women (*n*)	152	558	1795	3473	4825	1908	138	12,849		
Total energy kcal/day	1645±492	1753±503	1784±499	1804±530	1854±580	1820±583	1758±576	1818±553		
CHD g/day (%)	230.4 (55.9%)	245.8 (56.2%)	251.3 (56.6%)	257.1 (57.4%)	263.3 (57.4%)	259.5 (57.8%)	254.2 (58.7%)	258.1 (57.3%)		
Protein g/day (%)	58.7 (14.3%)	64.4 (14.7%)	67.8 (15.2%)	72.0 (15.9%)	77.4 (16.6%)	75.7 (16.5%)	72.9 (16.4%)	73.5 (16.1%)		
Fat g/day (%)	49.4 (26.9%)	51.6 (26.4%)	52.6 (26.3%)	52.4 (25.8%)	53.9 (25.7%)	52.9 (25.5%)	50.3 (24.9%)	53.0 (25.8%)		
SFA	14.4 (7.8%)	14.3 (7.3%)	14.0 (7.0%)	13.6 (6.7%)	13.8 (6.6%)	13.5 (6.5%)	12.9 (6.4%)	13.7 (6.7%)		
MUFA	16.8 (9.2%)	17.6 (9.0%)	18.0 (9.0%)	17.6 (8.6%)	17.9 (8.5%)	17.6 (8.4%)	16.7 (8.2%)	17.7 (8.6%)		
PUFA	11.8 (6.5%)	12.9 (6.6%)	13.5 (6.8%)	13.8 (6.8%)	14.4 (6.9%)	14.2 (6.9%)	13.3 (6.6%)	14.0 (6.8%)		
n-6PUFA	9.7 (5.3%)	10.5 (5.4%)	10.7 (5.3%)	10.4 (5.1%)	10.6 (5.1%)	10.5 (5.1%)	9.7 (4.8%)	10.5 (5.1%)		
n-3PUFA	2.4 (1.0)	2.7 (1.2)	3.0 (1.3)	3.2 (1.6)	3.5 (1.8)	3.4 (1.8)	3.2 (1.9)	3.3 (1.7)		
αlinolenic acid	1.6 (0.9%)	1.7 (0.9%)	1.8 (0.9%)	1.8 (0.9%)	1.8 (0.9%)	1.8 (0.9%)	1.7 (0.8%)	1.8 (0.9%)		
EPA+DHA	0.8 (0.4%)	1.0 (0.5%)	1.2 (0.6%)	1.4 (0.7%)	1.6 (0.8%)	1.6 (0.8%)	1.5 (0.7%)	1.5 (0.7%)	†	
n6/n3 ratio	4.2±0.8	4.0±0.8	3.8±0.9	3.4±0.9	3.3±1.0	3.3±1.0	3.3±1.0	3.4±1.0	†	
Cholesterol mg/day	293±122	304±132	317±137	328±162	350±181	347±184	341±174	336±169		
Salt g/day	9.6±3.0	10.8±3.4	11.5±3.5	12.5±4.1	13.6±4.5	13.6±4.6	13.3±4.6	12.8±4.3	†	

Data are expressed as means±standard deviations. Amount of daily intake of dietary variables (carbohydrate, protein and fat) are expressed as means (percentages of total energy). †and ‡ are explained in Table 2.
Abbreviations: CHD, carbohydrate; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n6/n3 ratio, ratio of n-6PUFA to n-3PUFA in the diet.

mean UACRs were positively associated with age in both sexes (trend $p<0.01$).

Table 6 shows age- and sex-specific prevalences of AF. For comparison with prevalences of AF in other studies, results of National Surveys in Japan [13], the CHF study [14], a study in Minnesota [15], and a study in Australia [16] are also shown. Prevalence of AF in subjects aged 18 years or older in this study was 1.56%. Prevalence of AF increased with advance of age in both men and women (from 0.1% in subjects younger than 40 years of age to 4.2% in subjects aged 80 years or older). Prevalence of AF in males aged 18 years or older was higher than that in females aged 18 years or older (3.29% vs 0.64%, $p<0.001$), and all age-specific prevalences of AF in males except for prevalences in the 20's and 80's groups were significantly higher than those in females (p values <0.001).

Table 7 shows a comparison of risk factors in non-hypertensive subjects and hypertensive subjects (with or without medication). Since mean age was higher in hypertensive subjects than in non-hypertensive subjects, comparison of each variable between the groups was performed after age adjustment. Blood pressure control was acceptable in hypertensive subjects taking anti-hypertension medication, while it was poorly controlled in hypertensive subjects without medication (mean SBP levels: 151.9 mmHg in men and 150.5 mmHg in women). Prevalences of obesity and DM were significantly higher in hypertensive subjects than those in non-hypertensive subjects after age adjustment (all p values <0.05).

4. Discussion

Cross-sectional analysis in this study revealed sex- and age-specific prevalences of hypertension, dyslipidemia, diabetes, and obesity in the general population living in a rural area of the northeastern part of Japan. The analysis also showed proportions of smokers, regular drinkers and subjects who do regular exercise.

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Table 5
Age- and sex-specific mean levels of new predictive markers (hsCRP, BNP, UACR)

Age group		18–29	30–39	40–49	50–59	60–69	70–79	≥80	Total	Trend	Sex difference
Men											
hsCRP	(*n*)	83	211	799	1500	3218	2776	371	8958		
Crude mean	(mg/L)	0.95 (2.84)	0.83 (1.95)	0.87 (1.87)	0.96 (2.15)	1.43 (4.80)	1.72 (5.91)	2.25 (7.53)	1.41 (4.78)	†	‡
Exclude high CRP[a]	(*n*)	82	210	795	1487	3158	2710	355	8797		
Crude mean	(mg/L)	0.66 (1.08)	0.71 (0.97)	0.77 (1.16)	0.80 (1.16)	0.94 (1.25)	1.01 (1.32)	1.13 (1.35)	0.92 (1.25)	†	‡
BNP (*n*)		46	131	597	1028	2134	1789	242	5967		
Crude mean	(pg/mL)	3.5 (5.8)	5.8 (6.6)	7.4 (9.4)	14.1 (21.6)	24.9 (34.4)	38.1 (56.2)	71.0 (117.9)	26.5 (47.1)	†	‡
High BNP[b]	(%)	0.0%	0.0%	0.8%	3.8%	10.9%	20.7%	47.5%	12.8%	†	‡
U-Alb (*n*)		83	211	796	1494	3199	2763	361	8907		
Crude mean	(mg/L)	10.9 (11.4)	30.0 (122.7)	28.5 (137.5)	35.0 (136.8)	46.2 (228.9)	53.9 (179.1)	74.9 (208.7)	45.6 (189.3)	†	‡
UACR	(mg/g)	8.4 (7.9)	24.5 (90.8)	27.8 (136.0)	37.3 (122.9)	56.4 (265.7)	67.5 (257.5)	101.0 (340.0)	54.7 (235.1)	†	‡
Exclude macroalbuminuria[c]		83	208	788	1462	3097	2656	336	8630		
Crude mean	(mg/L)	10.9 (11.4)	18.8 (37.9)	17.6 (34.8)	20.7 (34.0)	24.1 (42.7)	29.3 (48.6)	34.3 (55.4)	24.7 (43.2)	†	‡
UACR	(mg/g)	8.4 (7.9)	15.1 (32.7)	16.7 (28.4)	22.8 (36.1)	26.5 (40.0)	32.3 (44.6)	35.2 (43.7)	26.7 (40.1)	†	
% of microalbuminuria[d]		1.2%	6.7%	10.2%	18.3%	22.0%	28.1%	31.8%	22.0%	†	
Women											
hsCRP	(*n*)	179	618	1953	3955	5977	3893	395	16,970		
Crude mean	(mg/L)	0.70 (1.70)	0.78 (2.32)	0.72 (1.94)	0.86 (2.88)	1.07 (3.00)	1.23 (3.75)	1.27 (2.66)	1.01 (3.03)	†	
Exclude high CRP[a]	(*n*)	177	612	1940	3920	5895	3832	387	16,763		
Crude mean		0.56 (1.16)	0.61 (1.04)	0.60 (1.06)	0.68 (1.04)	0.78 (1.11)	0.86 (1.17)	0.97 (1.35)	0.75 (1.11)	†	
BNP	(*n*)	79	319	1415	2743	4003	2599	240	11,398		
Crude mean	(pg/mL)	8.3 (7.4)	9.6 (9.0)	13.9 (13.5)	16.1 (15.9)	23.8 (22.9)	35.7 (35.0)	58.9 (60.1)	23.7 (26.8)	†	
High BNP[b]	(%)	0.0%	0.3%	1.8%	2.5%	9.2%	21.2%	42.1%	9.8%	†	
U-Alb	(*n*)	176	610	1932	3918	5938	3856	385	16,815		
Crude mean	(mg/L)	17.0 (43.6)	14.5 (36.9)	17.7 (74.4)	17.9 (59.5)	24.7 (85.3)	36.5 (136.0)	52.9 (111.2)	25.2 (93.2)	†	
UACR	(mg/g)	16.9 (55.7)	16.6 (36.5)	23.3 (83.5)	28.7 (86.5)	39.9 (131.1)	58.0 (205.0)	87.4 (249.0)	39.5 (141.3)	†	
Exclude macroalbuminuria[c]		175	607	1916	3884	5841	3754	364	16,541		
Crude mean	(mg/L)	14.3 (23.2)	12.8 (26.3)	13.6 (23.9)	14.2 (24.3)	17.6 (26.9)	22.9 (31.0)	34.3 (45.6)	17.7 (27.8)	†	
UACR	(mg/g)	12.9 (19.5)	14.8 (25.7)	17.8 (27.0)	22.5 (31.2)	28.2 (36.6)	35.2 (41.2)	47.2 (53.2)	27.0 (36.2)	†	
% of microalbuminuria[d]		6.3%	6.1%	12.0%	17.2%	24.8%	34.7%	47.0%	23.4%	†	

Data are expressed as means (standard deviations) or percentages. †and ‡ are explained in Table 2. Abbreviations: hsCRP, high-sensitivity c-reactive protein; (*n*), number of participants; BNP, Brain natriuretic peptide; U-Alb, urine albumin concentration; UACR, urine albumin-creatinine ratio.

[a] Excluding high hsCRP level (≥10 mg/L).

[b] Proportion of high BNP level (≥50 pg/mL).

[c] Excluding macroalbuminuria (UACR ≥300 mg/g).

[d] Proportion of microalbuminuria (≥30 mg/g).

The results of a nutrition survey in the study indicated that attention must be given to dietary intake of salt. The incidence of stroke is higher in Japan than in the US and northern European countries [17], the prevalence of hypertension is higher and dietary intake of salt in Japan is also higher than that in other countries [2,17,18]. The results of our study indicate that the problem of excessive dietary intake of salt in the rural area in northeastern Japan should be resolved immediately.

This study provided sex- and age-specific mean levels of new predictive markers in the Japanese northeastern population. To our knowledge, there is no report on estimated sex- and age-specific levels of new predictive markers in apparently healthy subjects in a large population (>10,000 subjects). There were several interesting findings in this study. First, levels of new predictive markers in elderly people were significantly higher than those in middle-aged persons, and we should pay attention to the significant difference in each marker between middle-aged and elderly persons. Cut-off points should be determined with consideration given to generation difference in each predictive marker.

With regard to hsCRP levels, the mean level in each age group was about 0.1 mg/L in both sexes. Male subjects had higher hsCRP levels than those in females. Levels of hsCRP in this study were lower than those in western people. Previous studies in the Japanese general population also showed lower hsCRP levels in Japanese people than those in western people and they also showed lower levels in female subjects [19].

A few studies have shown sex- and age-specific levels of BNP in the general population [20–22]. Redfield et al. determined plasma BNP levels in a total of 2042 subjects in Minnesota [21]. They used two analytical methods: Biosite and Shionogi (the same method as that used in our study). They showed that BNP levels increased with age and were higher in

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Table 6
Age- and sex-specific prevalences of atrial fibrillation in this study and other studies

Age group	30–35	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	≧80	Trend	Sex difference
Men													
Iwate	0.5%		0.7%		1.3%		3.2%		5.2%		5.5%	†	‡
Japan National Surveys	0.1%		0.3%		0.7%		1.3%		3.8% (≧70)				
CHS study	–	–	–	–	–	–	–	5.9%	5.8%	5.8%	8.0%		
Australia	–	–	–	–	–	–	1.1%	3.3%	8.6%	15.0%	15.0%		
Minnesota	–	0.0%		0.5%		1.0%			6.0%	16.1%			
Women													
Iwate	0.0%		0.1%		0.2%		0.5%		1.4%		3.0%	†	
Japan National Surveys	0.0%		0.1%		0.4%		0.9%		2.2% (≧70)				
CHS study	–	–	–	–	–	–	–	2.8%	5.9%	5.9%	6.7%		
Australia	–	–	–	–	–	–	2.3%	2.7%	5.5%	8.4%	8.4%		
Minnesota	–	0.0%		0.5%		1.5%		3.0%		12.2%			

Sex- and age-specific prevalences are expressed as percentages.
†, $p<0.05$ by linear trend test. ‡ means significantly higher than that in the other sex after direct age adjustment.

women than in men. They also showed the median level in each age group (45–54, 55–64, 65–74, and 75–83 years) separately by sex. However, the skewed distribution of BNP levels and small number of subjects in each age group (2 to 194 subjects) made it difficult to determine mean levels and ranges of each group. We showed age- and sex-specific mean levels of BNP without excluding any subjects. Moreover, our data revealed that sex difference in BNP levels inverted at the age of 60 years. Male subjects less than 60 years of age had lower levels of BNP than those in female subjects in the same age group, but male subjects aged 60 years or older had higher levels of BNP than those in females. The reasons why younger males had lower BNP levels and why older males had higher levels of BNP than those in females are unclear.

Presence of microalbuminuria is a significant predictor for development of CVD [23–28]. The proportions of persons with microalbuminuria in a general population or in subjects without heart failure have been estimated in several studies.

Table 7
Comparison of risk factors in non-hypertensive subjects and hypertensive subjects (with/without medication)

	Male subjects			Female subjects		
	HTN (−)	HTN (+) and Med (+)	HTN (+) and Med (−)	HTN (−)	HTN (+) and Med (+)	HTN (+) and Med (−)
Subjects (*n*)	4899	2277	1843	10,568	4210	2376
Age (means±SDs)	61.1±12.5	68.6±7.8	65.2±10.1	57.9±11.9	67.4±8.1	64.3±9.5
Age-adjusted mean levels of each variable (95% confidence interval). Estimated variables for persons aged 60 years						
SBP (mmHg)	118.4 (118.0–118.8)	137.2 (136.6–137.8)	151.2 (150.6–151.8)	115.3 (115.0–115.6)	133.8 (133.3–134.2)	150.5 (150.0–151.1)
BMI (kg/m^2)	23.5 (23.4–23.6)	25.0 (24.9–25.1)	24.3 (24.2–24.8)	23.3 (23.3–23.4)	25.4 (25.3–25.5)	24.7 (24.6–24.8)
TC (mg/dL)	191.1 (190.2–192.0)	191.1 (190.0–192.5)	195.6 (194.1–197.1)	204.0 (203.4–204.6)	202.4 (201.4–203.5)	209.4 (208.1–210.7)
HDLC (mg/dL)	56.0 (55.6–56.4)	55.5 (54.8–56.2)	57.0 (56.3–57.7)	62.2 (61.9–62.5)	59.7 (59.3–60.2)	60.6 (60.0–61.2)
LDLC (mg/dL)	114.3 (113.5–115.1)	112.7 (111.4–114.0)	115.3 (113.9–116.6)	122.3 (121.7–122.9)	121.6 (120.6–122.5)	127.2 (126.1–128.4)
HbA_{1C} (%)	5.09 (5.07–5.11)	5.16 (5.13–5.19)	5.13 (5.10–5.17)	5.06 (5.05–5.07)	5.17 (5.15–5.19)	5.09 (5.07–5.12)
Proportions of subjects with each risk factor (%) and age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs)						
BMI≥25	28.2%	44.3%	37.3%	27.8%	53.8%	44.6%
OR (95%CI)	1.0	2.4 (2.1–2.7)	1.7 (1.5–1.9)	1.0	2.9 (2.7–3.2)	2.0 (1.9–2.2)
BMI≥30	2.1%	4.5%	3.4%	3.0%	10.6%	7.6
OR (95%CI)	1.0	3.4 (2.5–4.7)	2.1 (1.5–3.0)	1.0	4.8 (4.1–5.7)	3.1 (2.5–3.7)
DM	5.9%	11.1%	8.0%	2.7%	7.0%	4.2%
OR (95%CI)	1.0	1.8 (1.5–2.1)	1.3 (1.1–1.6)	1.0	2.1 (1.7–2.5)	1.3 (1.0–1.6)
DL	29.9%	30.7%	30.9%	35.6%	41.7%	45.4%
OR (95%CI)	1.0	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.0	1.0 (0.9–1.1)	1.3 (1.2–1.4)

Data are expressed as means±standard deviations, or age-adjusted means (95% confidence intervals), proportions (percentages), or age-adjusted odds ratios (ORs). Age-adjusted means (95% CIs) of continuous variables were estimated by using ANCOVA. Age-adjusted ORs (95%CIs) were estimated by logistic regression analysis. Abbreviations: MED (+), subjects with medication; MED (−), subjects without medication. Other abbreviations are the same as those in Table 2.

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Foster et al. showed that the proportion of persons with microalbuminuria was 12.2% in a general population from the data of Framingham Offspring Cohort Study [29]. Bramlage et al. reported that 19.0% of 39,125 patients who visited primary-care practices had microalbuminuria [30]. These two studies showed that the presence of microalbuminuria increased with an increase in SBP. In our study, prevalences of microalbuminuria in male subjects and female subjects were 22.0% and 23.4%, respectively. Mean levels of UACR and proportions of microalbuminuria increased with advance of age after adjusting for risk factors (SBP, BMI, TC,HDLC, HbA_{1c}, and smoking). In our study, male subjects less than 60 years of age had higher levels of UACR than those in female subjects in the same age group, but male subjects aged 60 years or older had lower levels of UACR than those in females. Crude mean levels of urinary albumin were higher in men than in women in all age groups. This phenomenon may be attributable to lower levels of urinary creatinine in elderly women. Thus, attention should be given to possible overestimation in elderly women.

This study provided sex- and age-specific prevalences of AF in a rural area of northeastern Japan. A previous study showed that age- and sex-specific prevalences of AF in adults in Japan were lower than those in western countries in both sexes [13]. Age- and sex-specific prevalences of AF in males in this study are similar to those in the CHF study [14] and lower than those in other studies in western countries [15,16]. Sex- and age-specific prevalences in females in this study were lower than those in the Japan National Survey and in western countries [14–16]. The higher prevalence of AF in males in the present study than that in the National Survey in Japan [13] may be due to high prevalence of predisposing factors for AF, such as hypertension, diabetes, and obesity, compared to the prevalence of those factors in past national surveys in Japan.

Comparison of risk factors between three groups (non-hypertensive subjects, hypertensive subjects with medication, hypertensive subjects without medication) revealed that there was well-controlled blood pressure in subjects with medication and poorly controlled blood pressure in subjects without medication in the study area. Hypertensive subjects who did not take anti-hypertension medication accounted for about 20% of total subjects and their blood pressure remained poorly controlled. Moreover, hypertensive subjects with or without medication have higher prevalences of obesity, DM, and dyslipidemia than those in non-hypertensive subjects. The risk for future development of CVDs in subjects with hypertension is expected to be very high. These findings indicate the need for activities to prevent future development of CVD in the study area.

We tried to compare CVD risk factor-related variables in subjects in the present study and subjects in the Japan National Survey. Since there was a significant difference in age distribution between the two populations, we tried to show proportions of subjects having hypertension in each sex-and age-specific group. However, sex-and age-specific proportion of subjects in each blood pressure category was expressed as percentage without consideration of subjects with/without medication in the Japan National Survey [2,3]. Simple comparison of each sex- and age-specific prevalence of elevated blood pressure (SBP $\geq$ 140 or DBP $\geq$ 90) between our study and the Japan national surveys showed that proportions of subjects with elevated blood pressure were lower in our study than those in the Japan national surveys (data are not shown). This comparison appears to be meaningless. Comparison should be done with due consideration of the proportion of subjects taking anti-hypertension medication. Nonetheless, more than half of the people aged 60 years or older living in the study area have hypertension, and we should pay attention to cardiovascular morbidity and mortality in this area.

Several limitations to our study should be noted. A single instance of blood sampling may be susceptible to short-term variation. Since determination of dietary variables was based on a self-administered questionnaire, levels of dietary intake of energy and each nutrient estimated by a computer algorithm are not always consistent with true absolute values. However, it is reasonable to compare levels of dietary intake of nutrients in several groups when estimations of dietary intake of nutrients have been performed in a unified way. Persons who did not participate in the annual health check-ups were probably in poor condition and might have had CVD. These factors might have reduced the number of participants with CVD in this study; thus, the prevalences of CVD including hypertension, MI, stroke, and AF might be underestimated.

In conclusion, the results of this study showed high prevalences of cardiovascular risk factors in the study area. Attention should be given to cardiovascular risk factors, especially in people living in a rural area of northeastern Japan, in order to prevent future development of CVD.

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M.O. had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Appendix A. Members of the Iwate-KENCO Study

Chairman: Akira Okayama (The First Institute of Health Service, Japan Anti-Tuberculosis Association, Tokyo).

Principal investigators: Akira Ogawa (Department of Neurosurgery, School of Medicine, Iwate Medical University, Morioka), Motoyuki Nakamura (Department of Internal Medicine II, School of Medicine, Iwate Medical University,

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Morioka), Yasuo Terayama (Department of Neurology, School of Medicine, Iwate Medical University, Morioka), Kazuyoshi Itai, Toshiyuki Onoda, Masaki Ohsawa, Kozo Tanno, Kiyomi Sakata, (Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Morioka), Mitsumasa Tazawa (Morioka Public Health Care Center), Kazuko Kawamura (Iwate Health Service Association), Toru Kuribayashi (Department of Health and Physical Education, Faculty of Education, Iwate University, Morioka), Yuki Yoshida (Department of Neurosurgery, School of Medicine, Iwate Medical University, Morioka), Tetsuo Hebiguchi, Hiroki Matsudate (Research Institute for Environmental Sciences and Public Health of Iwate Prefecture), and Seiji Yasumura (Department of Public Health, School of Medicine, Fukushima Medical University, Fukushima).

Research associate members: Shinji Makita (Department of Internal Medicine II, School of Medicine, Iwate Medical University, Morioka), Yasuhiro Ishibashi (Department of Neurology, School of Medicine, Iwate Medical University, Morioka), Kenji Takashima, Yoko Tonari (Iwate Health Service Association), Shin-ichi Omama (Department of Neurosurgery, School of Medicine, Iwate Medical University, Morioka), and Hirohide Yokokawa (Department of Public Health, School of Medicine, Fukushima Medical University, Fukushima).

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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

Shinji Makita [a,*], Motoyuki Nakamura [a], Kenyu Satoh [a], Fumitaka Tanaka [a], Toshiyuki Onoda [b], Kazuko Kawamura [e], Masaki Ohsawa [b], Kozo Tanno [b], Kazuyoshi Itai [b], Kiyomi Sakata [b], Akira Okayama [f], Yasuo Terayama [c], Yuki Yoshida [d], Akira Ogawa [d]

[a] Department of Internal Medicine II and Memorial Heart Center, Iwate Medical University, 19-1 Uchimaru, Morioka 0208505, Japan
[b] Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Japan
[c] Department of Neurology, Iwate Medical University, Morioka, Japan
[d] Department of Neurosurgery, Iwate Medical University, Morioka, Japan
[e] Iwate Health Service Association, Morioka, Japan
[f] The First Institute of Health Service, Japan Anti-Tuberculosis Association, Osaka, Japan

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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.

* Corresponding author. Tel.: +81 19 651 5111x2324; fax: +81 19 651 7072.
E-mail address: makitas@seagreen.ocn.ne.jp (S. Makita).

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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.

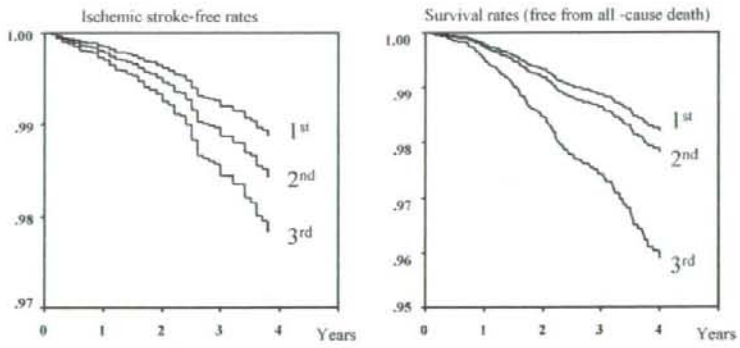

Fig. 1. Cumulative ischemic stroke-free rates and survival rates by age-adjusted Cox regression model for hs-CRP tertiles.

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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)*	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.
* 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.

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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.

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Conflict of interest

The authors report no conflicts of interest.

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