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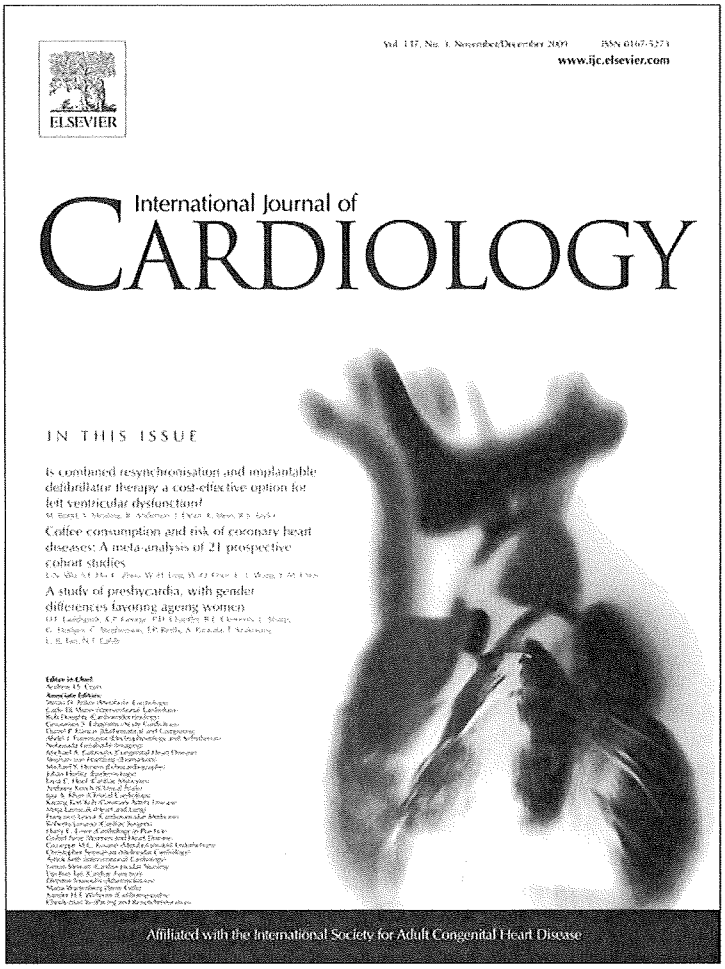

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Cardiovascular risk factors in the Japanese northeastern rural population ☆

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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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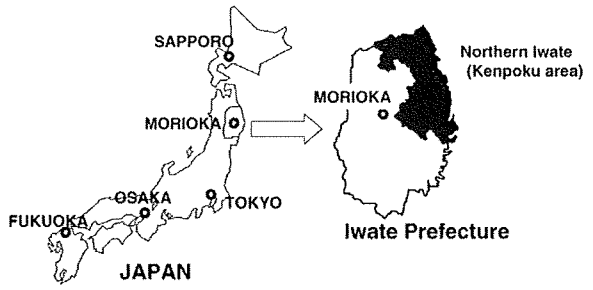

Fig. 1. The study area. This figure shows a map of Japan and a map of Iwate Prefecture. Iwate Prefecture is located in the northeastern part of the main island (Honshu Island) of Japan. The black area of Iwate Prefecture indicates the study area. Kenpoku means northern part of the prefecture in Japanese.

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.

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.

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.

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

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.

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	(ρg/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	(ρg/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

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.

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.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

Appendix A. Members of the Iwate-KENCO Study

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Gender-specific risk stratification with plasma B-type natriuretic peptide for future onset of congestive heart failure and mortality in the Japanese general population

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Abstract

Background: Elevated plasma B-type natriuretic peptide (BNP) levels suggest a high risk for future onset of cardiovascular events including congestive heart failure (CHF) and mortality. In the general population, although median plasma BNP levels have been reported to be higher in women than in men, the incidence of CHF and mortality are lower in women. However, no studies have examined gender-specific risk stratification of plasma BNP levels for future onset of CHF and mortality.
Methods: Subjects of this study were recruited from our general population. Baseline data including plasma BNP were determined in 13,466 subjects (men 4527, women 8939; median age = 64 yrs). A multivariate Cox regression analysis was performed to examine the predictive ability of plasma BNP for new onset of CHF and mortality.
Results: The mean follow-up duration was 2.9 years. After adjustment for traditional cardiovascular risk factors including atrial fibrillation, hazard ratios for CHF development for values above the 75th percentile of BNP were 13.4 ($p<0.001$) in men and 8.5 ($p<0.001$) in women. Similarly, each increment of 1SD in log BNP levels increased the hazard ratio by 8.8 ($p<0.001$) in men, and 6.7 ($p<0.001$) in women. The area under the receiver operating characteristic curve was significant for prediction of the onset of CHF (men; 0.853, women; 0.838). In addition, increased plasma BNP levels implied high risk of any-cause mortality in men (above the 75th percentile; hazard ratio = 1.8, $p=0.005$: increment of 1SD; hazard ratio = 1.4, $p=0.024$), but this relationship was suboptimal in women.
Conclusion: Measurements of plasma BNP provides strong predictive information about future onset of CHF in both sexes, with predictive ability for death being effective especially in men.

Keywords: Mortality; Community; Non-white; Japanese

B-type natriuretic peptide (BNP) has been recognized as a hormone released with its biologically inactive N-terminal peptide (NT-proBNP) from the heart [1,2]. It has been suggested that cardiac secretion of BNP is increased by elevated left ventricular end-diastolic pressure, decreased

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cardiac systolic/diastolic function, hypertensive heart disease, atrial fibrillation, and myocardial ischemia [3–7]. It is therefore expected that measurement of plasma BNP levels would provide useful information for identification of subjects at high risk of CHF due to various phenotypes of structural heart disease [8,9].

In fact, Wang et al. have shown for the first time that a 1standard deviation increment in plasma BNP as well as elevated plasma BNP above the 80th percentile was associated with a significant increase in the risk of new onset of CHF and any-cause mortality in the Framingham general population [10]. Similar positive associations between plasma NT-proBNP levels and risk of cardiovascular events including onset of CHF and mortality have been reported in the Danish general population [11]. These previous studies have suggested that plasma levels of BNP or NT-proBNP may serve as a possible screening tool for subjects at high risk of CHF and death within the general population. However, few studies have examined the utility of plasma BNP measurement as a predictor of future onset of CHF by a sex-stratified analysis, because women have a relatively lower incidence of CHF and higher median plasma BNP levels than men [12–14].

Moreover, subjects of previous studies were mainly drawn from white populations [10,11]. No studies have confirmed the relationship between plasma BNP levels and cardiovascular events and mortality in community-based cohorts taken from non-white populations. The incidence and prevalence of cardiovascular events including CHF has been reported to differ among ethnic groups [15]. In the general population, several reports have shown that plasma BNP levels are affected by anthropometric factors such as body mass index [16] and genetic features [17], and this may alter the utility of plasma BNP measurement as a predictor of cardiovascular events.

These suggest that the relationship between plasma BNP levels and cardiovascular outcomes should be evaluated separately in men and women, and it may also be important to examine whether the relationship is applicable in other ethnic populations. The present study has therefore sought to determine whether 1) plasma BNP levels are associated with an increased risk of CHF and any-cause death in both sexes in the general population; and 2) the relationship between plasma BNP and cardiovascular outcome observed in the white population is valid in other ethnic groups, specifically the Japanese population.

1. Methods

1.1. Study population

The original cohort of the Iwate-KENCO study was recruited from the community-dwelling population living in the three districts (Ninohe, Kuji, and Miyako) of the northern Iwate prefecture, Japan. This region has a resident population of over 144,000 adults over the age of 40 years based on census data from October 2005. The cohort was recruited from subjects of a government-regulated multiphasic health checkup for the general population. Invitations to participate in the multiphasic health screening program were issued by government offices in each municipality.

The total number of participants who agreed to join the Iwate-KENCO study in the three districts was 26,469 (original cohort). The acceptance rate for participation from government-regulated health screening was 84.5%. Of the original cohort living in Ninohe and Kuji districts (n=15,927), 15,394 subjects (97%) had BNP measurements (BNP cohort: men 5288; women 10,106). Subjects were excluded from this cohort for the following reasons: age under 40 (575), history of cardiovascular events such as myocardial infarction, stroke or heart failure (507), and missing covariates (846). The final statistical analysis was therefore performed on 13,466 subjects (men 4527; women 8939: Table 1). This study protocol was approved by our university ethics committee and local institutional review committees. All participants gave written informed consent.

Table 1
Baseline characteristics of study population, the Iwate KENCO study

	Men	Women
Number	4527	8939
Age (years)		
Mean (±SD)	64.1±10.3	62.0±10.0
Median	66.0	63.0
Plasma BNP (pg/ml)		
1st quartile	<6.5	<8.9
2nd quartile	6.5–14.8	8.9–17.1
3rd quartile	14.8–30.0	17.1–30.4
4th quartile	≥30.0	≥30.4
Systolic blood pressure (mmHg)		
Mean (±SD)	130.1±19.4	125.5±19.7
Median	128.5	123.5
Diastolic blood pressure (mmHg)		
Mean (±SD)	77.8±10.8	73.7±10.8
Median	77.5	73.0
Hypertension (%)	44.4	38.8
Antihypertensive drugs (%)	23.6	24.3
Body mass index (kg/m2)		
Mean (±SD)	23.9±2.9	24.1±3.4
Median	23.8	23.9
Atrial fibrillation (%)	3.0	0.6
HbA1c (%)		
Mean (±SD)	5.2±0.8	5.1±0.6
Median	5.0	5.0
Diabetes (%)	8.0	4.3
Antidiabetic medication (%)	4.6	2.4
Total cholesterol (mg/dl)		
Mean (±SD)	193.2±32.6	206.7±31.8
Median	191.0	206.0
Hypercholestrolemia (%)	10.3	20.3
Antihypercholestrolemic drugs (%)	2.8	7.3
HDL-cholesterol (mg/dL)		
Mean (±SD)	56.4±15.4	61.8±14.5
Median	54.0	60.0
Current smoking (%)	33.4	2.5
Regular alcohol intake (%)	61.7	11.1
Regular exercise (%)	17.0	10.5

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1.2. BNP assay

Non-fasting blood samples were drawn from the antecubital vein while participants were seated. Blood samples were collected into vacuum tubes. While blood samples for routine blood testing were being taken, an additional 2 ml sample of venous blood was collected into a test tube containing EDTA-2Na for plasma BNP measurement. Tubes were stored immediately after sampling in an icebox and transported to the Iwate Health Service Association laboratory each afternoon. They were then centrifuged at 1500 g for 10 min. After separation, plasma samples were stored frozen at −70 °C until transportation to the Shionogi central laboratory for the assay. Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi, Japan). Cross-reactivity of the antibody was 100% for human BNP and 0.001% for human atrial natriuretic peptide. Intra- and inter-assay coefficients of variation were 5% and 6%, respectively.

1.3. Risk factor definitions

Subjects used a self-reported questionnaire to document medical history including status (yes or no) of prescribed drugs for hypertension, diabetes, hypercholesterolemia, stroke, angina, CHF and myocardial infarction. Smoking habits (current or non-smoker), regular alcohol intake (yes or no), and regular exercise (≥60 min of exercise and ≥8 times per month) were also assessed by a questionnaire developed by the study committee. Systolic and diastolic blood pressures were determined with an automated sphygmomanometer with subjects seated for at least 5 min before measurement. Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, and/or the use of antihypertensive medication. Body height was measured with participants in stocking feet and weight was measured wearing light clothing. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Diabetes was ascertained by detection of a non-fasting glucose concentration ≥200 mg/dl and/or HbA1c value ≥6.5% [18] and/or a use of anti-diabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration ≥240 mg/dl and/or the use of anti-lipidemic medications.

1.4. Outcome

A follow-up survey assessing mortality, migration, and the incidence of CHF was carried out after the baseline study. Admission cases of CHF in the cohort were checked by the regional registration survey data for heart diseases, which records primary hospital discharge diagnoses in the study area. Details of this register have been described previously [15]. The cases of CHF were objectively defined by Framingham criteria [19]. All deaths and migration were confirmed by the official resident registration data issued by the local government offices.

1.5. Statistical analysis

Continuous variables are shown as median or mean. Owing to the purpose of the present study, the following analyses were performed separately in men and women. Participants were divided into quartiles according to their baseline plasma BNP levels. Survival from entry into the study was estimated using the Kaplan–Meier method, followed by a trend test (Log rank). We evaluated the association between baseline plasma BNP levels and two clinical endpoints (new onset of CHF and death from any cause). Using a Cox proportional hazards regression model, hazard ratios (HRs) for plasma BNP with each outcome were assessed. In these analyses, plasma BNP levels were used as a categorical variable and as continuous variables after natural logarithmic transformation. For the categorical analyses, we used prespecified thresholds corresponding to the 75th percentile values. In this multivariable proportional-hazards regression model, we adjusted analyses for age, body mass index, and the presence or absence of hypertension, diabetes, hypercholesterolemia, current smoking, regular exercise and atrial fibrillation. Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of plasma BNP throughout the range of concentrations as an indicator of CHF or all cause of mortality. The area under the curve and 95% confident interval (CI) of each ROC curve were calculated to provide a measure of the overall diagnostic accuracy of the test. All statistical analysis was performed using SPSS software. A significant difference was defined as $p<0.05$.

2. Results

2.1. Baseline characteristics of the cohort

The median age of male and female cohorts was 66 in men, and 63 in women, respectively (Table 1). The number of women participants was approximately twice the number of men. The median plasma BNP level was higher in women than men (17.1 pg/ml versus 14.8 pg/ml; $p<0.001$). The prevalence of hypertension, atrial fibrillation, diabetes, current smoking, regular alcohol intake tended to be higher in men than in women.

2.2. Congestive heart failure and all-cause death

During the 2.9 year follow-up period, there were 44 cases of new onset CHF (men=23; women=21). The crude incidence rate of CHF was 1.75/1000 person-years in men and 0.82/1000 person-years in women. In addition, a total of 182 participants died from any cause (men=106; women=76). The crude death rate was 8.07/1000 person-years in men and

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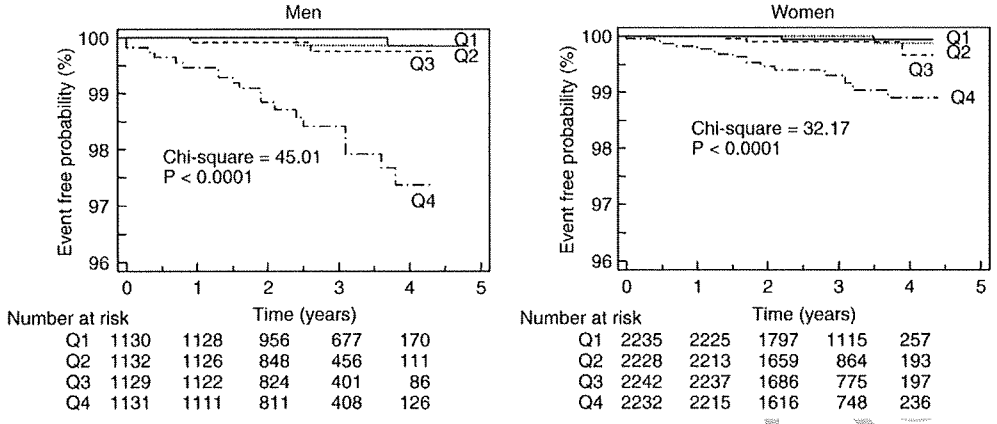

Fig. 1. Kaplan–Meier curves of unadjusted cumulative CHF free probabilities according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

2.98/1000 person-years in women. The event free probabilities for CHF according to BNP quartiles are shown in Fig. 1. In both sexes, the highest quartile showed the lowest event free rate for onset of CHF (p for trends: men, $p<0.0001$; women, $p<0.0001$). Similarly, mortality rate increased with increasing quartile levels of plasma BNP (p for trends: men, $p<0.0001$; women, $p=0.0014$) (Fig. 2).

2.3. Multivariate analysis of outcomes

Increased plasma BNP levels predicted new onset of CHF even after adjusting for cardiovascular risk factors such as age, atrial fibrillation, BMI, current smoking, diabetes, hypercholesterolemia, hypertension, regular alcohol intake, and exercise habit in both sexes. As shown in Table 2, male participants with plasma BNP values above the 75th percentile had 13.4-fold increased risk of onset of CHF (95% CI, 4.1 to 43.6; $p<0.001$) relative to those with values equal to or below. In women, the association between the risk of CHF and plasma BNP above the 75th percentile was also significant (hazard ratio = 8.5; 95% CI, 2.9 to 25.3: $p<0.001$). When plasma BNP was analyzed as a continuous variable, increasing plasma BNP for each 1SD increment in log BNP was associated with an increased risk of onset of CHF, with adjusting hazard ratios of 8.8 (95% CI, 3.9 to 20.1; $p<0.001$) in men and 6.7 (95% CI, 2.9 to 15.3; $p<0.001$) in women.

Median plasma BNP levels were higher in subjects complicated with atrial fibrillation than in subjects in sinus rhythm (men, 106.0 pg/ml versus 14.3 pg/ml; $p<0.001$: women, 118.0 pg/ml versus 17.0 pg/ml; $p<0.001$). To eliminate possible confounding effects of atrial fibrillation on the onset of CHF and plasma BNP, participants with atrial fibrillation at baseline were excluded from the analysis. The relationship between plasma BNP levels above the 75th percentile (categorical variable) and risk of CHF onset remained robust in both men (hazard ratio = 15.5; 95% CI, 4.5 to 53.9: $p<0.0001$) and women (hazard ratio = 7.9; 95% CI, 2.6 to 23.9: $p<0.001$) (Table 2). The risk of CHF for each 1SD increment in log BNP increased 12.8-fold in men (95% CI, 5.4 to 30.5; $p<0.0001$), and 7.5-fold in women (95% CI, 3.2 to 17.5; $p<0.001$) after exclusion of subjects with atrial fibrillation at baseline.

In men, the hazard ratio for mortality according to plasma BNP as a categorical variable (above the 75th percentile) was 1.8 (95% CI, 1.2 to 2.7; $p=0.005$). Also, a 1SD increment in plasma BNP as a log transformed value was associated with

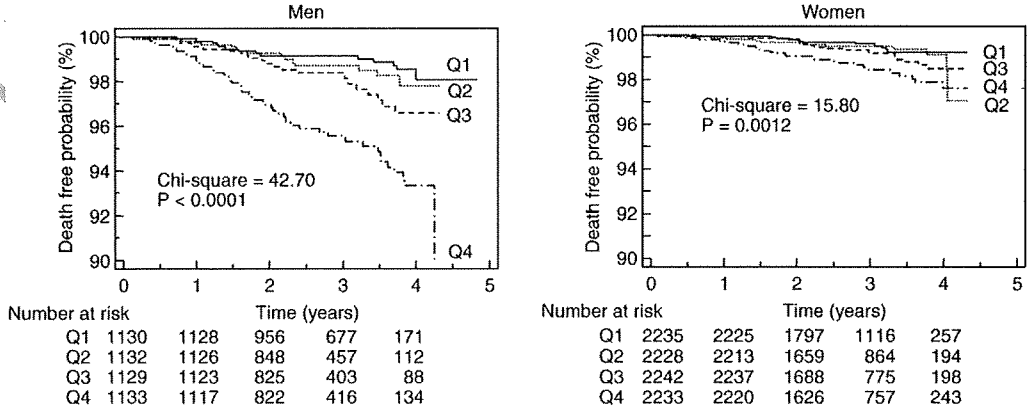

Fig. 2. Kaplan–Meier curves of unadjusted cumulative survival according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

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Table 2
Multivariate analysis of the association of plasma BNP levels, congestive heart failure and death

	Adjusted hazard ratio for BNP values above 75th percentile			Adjusted hazard ratio per 1SD increment in Log BNP		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Men						
Heart failure	13.45	4.15 to 43.56	0.001	8.84	3.88 to 20.13	0.001
Heart failure (ex. Afib)	15.50	4.46 to 53.88	0.001	12.85	5.41 to 30.51	0.001
All cause death	1.81	1.20 to 2.75	0.005	1.38	1.04 to 1.82	0.024
Women						
Heart failure	8.54	2.88 to 25.31	0.001	6.68	2.93 to 15.26	0.001
Heart failure (ex. Afib)	7.88	2.60 to 23.91	0.001	7.53	3.24 to 17.53	0.001
All cause death	1.22	0.76 to 1.98	0.408	1.17	0.90 to 1.53	0.231

The hazard ratios were adjusted for age, atrial fibrillation, BMI, current smoking, diabetes, hypercholesterolemia, hypertension, regular alcohol intake, and regular exercise: ex. Afib = analysis after exclusion of atrial fibrillation.

a significant (1.4-fold) increase in the hazard ratio for death (95% CI, 1.0 to 1.8; $p=0.024$) in men (Table 2). However, in women, the association between plasma BNP and mortality was not significant (above the 75th percentile, $p=0.41$: each 1SD increment, $p=0.23$).

2.4. ROC analysis

As shown in Fig. 3, the overall power of plasma BNP for prediction of CHF was significant. The optimal threshold of BNP for prediction of CHF was 32 pg/ml (sensitivity; 83%, specificity; 77%) in men, and 62 pg/ml (sensitivity; 67%, specificity; 94%) in women, respectively. The area under the ROC curve was 0.853 (95% CI, 0.842 to 0.863) in men, and 0.838 (95% CI, 0.830 to 0.845) in women, respectively. The predictive ability of plasma BNP for all-cause of death as represented by the area under the curve was lower than that for CHF (men; 0.665, women; 0.615).

3. Discussion

The present study has found that elevated plasma BNP in the middle aged and elderly general population serves as a significant indicator of high risk for future onset of CHF in both men and women. This relationship remains statistically robust even after adjustment for clinical risk factors for CHF and after exclusion of subjects having atrial fibrillation at baseline. In addition, increased plasma BNP is a useful biomarker for prediction of high risk for any cause mortality in men, whereas this relationship was obscure in women.

Wang et al. have reported that elevated levels of plasma BNP were a useful predictor of the risk of death and cardiovascular events including CHF in a mainly white US population living in Framingham [10]. The incidence of CHF is well known to be lower in women than in men. Conversely, median plasma BNP levels are reported to be higher in women than in men in the general population [12–14]. This appears to contradict the epidemiological fact of a lower prevalence of cardiovascular disorders in women. However, little information is available to show whether the relationship between plasma BNP and the risk of onset of CHF remains significant in both sexes. Subject numbers in these previous studies may have been insufficient for separate analysis of predictive values for CHF in each gender group. The present study has suggested for the first time that plasma BNP may be a feasible screening tool for identification of individuals at high risk of future development of CHF within an apparently healthy population without gender bias.

Moreover, there have been no reports about the predictive abilities of plasma BNP for any cardiovascular events in non-white populations having a different incidence of cardiovascular disease. The incidence of cardiovascular events including CHF differs among races, with the Japanese having a relatively lower rate [15,20–22]. Plasma BNP levels have been demonstrated to be affected by anthropometric factors such as body mass index [16], and to be modified by heritability and genetic factors in a community based sample [17]. These findings suggest that the distribution of plasma BNP in apparently healthy populations may differ among ethnicities and communities. It would therefore be important to confirm that the predictive ability of BNP for CHF reported in US and European populations could be extrapolated to other ethnic populations. The present study has established the relationship between plasma BNP levels and risk of CHF in a non-white, specifically Japanese, population. Thus the present study suggests that BNP testing may be useful even in a low-risk population.

In contrast to the value of plasma BNP for predicting future onset of CHF in either sex, the association between plasma BNP and all cause mortality was less robust after

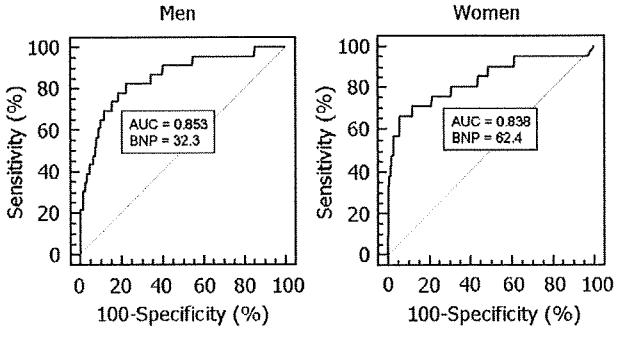

Fig. 3. Receiver-operating-characteristic curves of plasma BNP concentration to predict future onset of CHF.

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adjustment for cardiovascular risk factors especially in the female cohort. In several previous studies without gender-specific analysis, elevated plasma BNP or plasma NT-proBNP levels were associated with an increased risk of death in the general population [10,11,23,24]. The present study has confirmed this association in men only, with the reasons for the lack of predictive ability of BNP testing for all causes of death in women remained unknown. Although person-years among female subjects in the present study may not have been insufficient (>=25,000 person-years), the follow-up may have been shorter than those of earlier studies (>5 years). In addition, it seems that cardiovascular death rate among the present female cohort may have been lower due to the lower incidence of cardiovascular risk factors compared to the male cohort. These biases may account for the possible dissociation between mortality and plasma BNP in women.

3.1. Limitations

This study has several limitations. The capture of CHF during the follow-up period was restricted to hospitalized cases so that CHF patients treated at an outpatient clinic only may be missing from the follow-up data. As the Framingham criteria for CHF employed in this study tend to capture relatively advanced CHF, the observed predictive value of plasma BNP is assured in cases with clinically overt CHF. As echocardiographic parameters were not included in the baseline data, the reasons for the elevation of plasma BNP are not known. However, according to our previous cross-sectional cohort study of the general population, elevated plasma BNP concentrations has a significant sensitivity and specificity for screening several phenotypes of structural heart disease [8]. The predictive abilities of high plasma BNP levels may be due to the capability for selection of subjects who have underlying cardiac disorders which are prone to progress to overt CHF. More than 20% of our cohort was receiving antihypertensive agents at baseline. Several types of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers have been reported to reduce cardiovascular events and mortality in high risk subjects [25,26]. This type of drug also has been reported to reduce plasma levels of BNP [27]. In view of these findings, the present study did not assess the effects of these drugs on the incidence of outcomes or on plasma BNP levels. However, when the use of antihypertensive medication (yes or no) was entered into the multivariate regression model, the significance of the predictive ability of plasma BNP did not weaken for CHF (hazard ratios >5.0, $p<0.0001$; both above the 75th percentile level and each 1SD increment).

In conclusion, measurement of plasma BNP provides strong predictive information about future onset of CHF in both sexes, with the predictive ability for death effective especially in men.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [28].

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Plasma B-type Natriuretic Peptide Level and Cardiovascular Events in Chronic Kidney Disease in a Community-based Population

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