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

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

Motoyuki Nakamura [a,*], Fumitaka Tanaka [a], Toshiyuki Onoda [b], Tomohiro Takahashi [a], Toshie Segawa [a], Kazuko Kawamura [c], Kozo Tanno [b], Makaski Ohsawa [b], Kazuyoshi Itai [b], Kiyomi Sakata [b], Shinji Makita [a], Akira Okayama [d]
On behalf of the Iwate KENCO study groups

[a] *Departments of Internal Medicine, Iwate Medical University, Morioka, Japan*
[b] *Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Japan*
[c] *Iwate Health Service Association, Morioka, Japan*
[d] *Japan Anti-Tuberculosis Association, Tokyo, Japan*

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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

* Corresponding author. Department of Internal Medicine, Division of Cardiology, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan. Tel.: +81 19 651 5111e2321; fax: +81 19 626 4406.
E-mail address: nkmrmoto@iwate-med.ac.jp (M. Nakamura).

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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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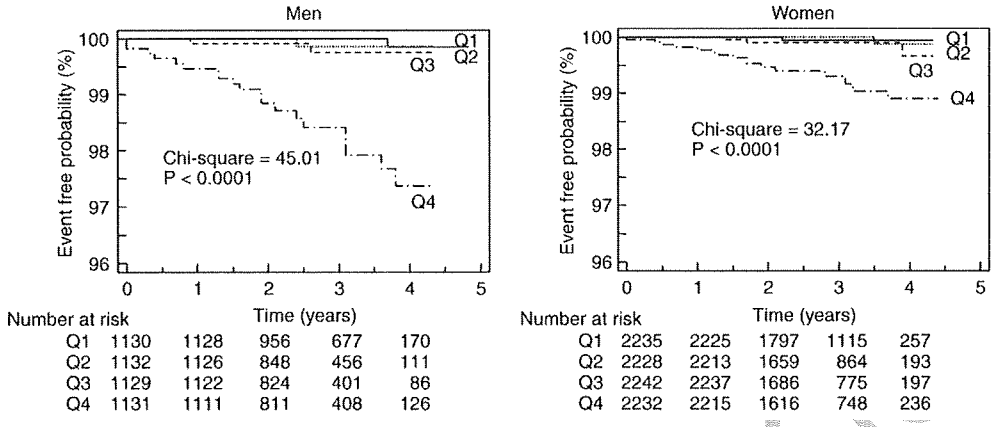

Fig. 1. Kaplan–Meier curves of unadjusted cumulative CHF free probabilities according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

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

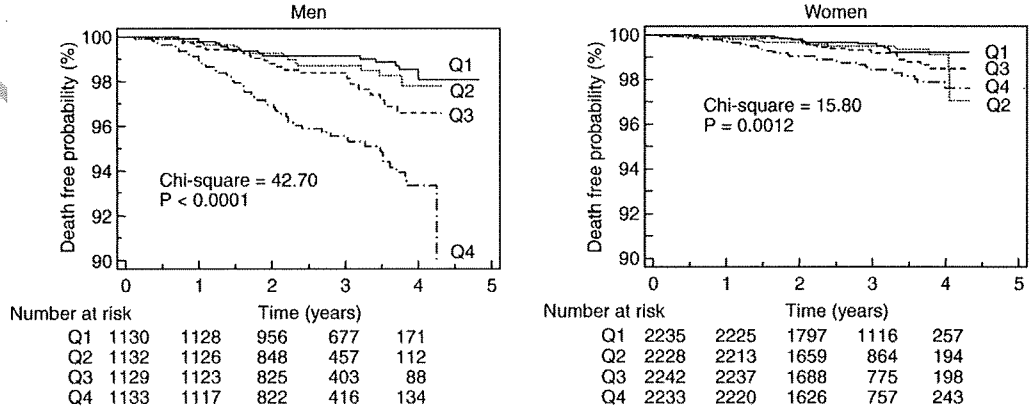

Fig. 2. Kaplan–Meier curves of unadjusted cumulative survival according to quartiles of plasma BNP at baseline in the general population. Q = quartile.

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t2.1 Table 2
t2.2 Multivariate analysis of the association of plasma BNP levels, congestive heart failure and death

t2.3		Adjusted hazard ratio for BNP values above 75th percentile			Adjusted hazard ratio per 1SD increment in Log BNP		
t2.4		HR	95%CI	*P* value	HR	95%CI	*P* value
	Men						
t2.6	Heart failure	13.45	4.15 to 43.56	0.001	8.84	3.88 to 20.13	0.001
t2.7	Heart failure (ex. Afib)	15.50	4.46 to 53.88	0.001	12.85	5.41 to 30.51	0.001
t2.8	All cause death	1.81	1.20 to 2.75	0.005	1.38	1.04 to 1.82	0.024
	Women						
t2.10	Heart failure	8.54	2.88 to 25.31	0.001	6.68	2.93 to 15.26	0.001
t2.11	Heart failure (ex. Afib)	7.88	2.60 to 23.91	0.001	7.53	3.24 to 17.53	0.001
t2.12	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 t2.13 fibrillation.

258 a significant (1.4-fold) increase in the hazard ratio for death
259 (95% CI, 1.0 to 1.8; $p=0.024$) in men (Table 2). However, in
260 women, the association between plasma BNP and mortality
261 was not significant (above the 75th percentile, $p=0.41$: each
262 1SD increment, $p=0.23$).

263 *2.4. ROC analysis*

264 As shown in Fig. 3, the overall power of plasma BNP for
265 prediction of CHF was significant. The optimal threshold of
266 BNP for prediction of CHF was 32 pg/ml (sensitivity; 83%,
267 specificity; 77%) in men, and 62 pg/ml (sensitivity; 67%,
268 specificity; 94%) in women, respectively. The area under the
269 ROC curve was 0.853 (95% CI, 0.842 to 0.863) in men, and
270 0.838 (95% CI, 0.830 to 0.845) in women, respectively. The
271 predictive ability of plasma BNP for all-cause of death as
272 represented by the area under the curve was lower than that
273 for CHF (men; 0.665, women; 0.615).

274 **3. Discussion**

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

284 Wang et al. have reported that elevated levels of plasma
285 BNP were a useful predictor of the risk of death and
286 cardiovascular events including CHF in a mainly white US
287 population living in Framingham [10]. The incidence of
288 CHF is well known to be lower in women than in men.
289 Conversely, median plasma BNP levels are reported to
290 be higher in women than in men in the general population
291 [12–14]. This appears to contradict the epidemiological fact
292 of a lower prevalence of cardiovascular disorders in women.
293 However, little information is available to show whether the
294 relationship between plasma BNP and the risk of onset of
295 CHF remains significant in both sexes. Subject numbers in
296 these previous studies may have been insufficient for
297 separate analysis of predictive values for CHF in each
298 gender group. The present study has suggested for the first
299 time that plasma BNP may be a feasible screening tool for
300 identification of individuals at high risk of future develop-
301 ment of CHF within an apparently healthy population
302 without gender bias.

303 Moreover, there have been no reports about the predictive
304 abilities of plasma BNP for any cardiovascular events in non-
305 white populations having a different incidence of cardiovas-
306 cular disease. The incidence of cardiovascular events
307 including CHF differs among races, with the Japanese
308 having a relatively lower rate [15,20–22]. Plasma BNP
309 levels have been demonstrated to be affected by anthropo-
310 metric factors such as body mass index [16], and to be
311 modified by heritability and genetic factors in a community
312 based sample [17]. These findings suggest that the distribu-
313 tion of plasma BNP in apparently healthy populations may
314 differ among ethnicities and communities. It would therefore
315 be important to confirm that the predictive ability of BNP for
316 CHF reported in US and European populations could be
317 extrapolated to other ethnic populations. The present study
318 has established the relationship between plasma BNP levels
319 and risk of CHF in a non-white, specifically Japanese,
320 population. Thus the present study suggests that BNP testing
321 may be useful even in a low-risk population.

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

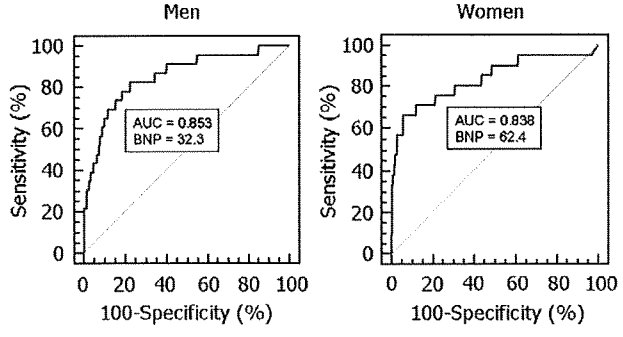

Fig. 3. Receiver-operating-characteristic curves of plasma BNP concentration to predict future onset of CHF.

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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

Masafumi Sakuma[1], Motoyuki Nakamura[1], Fumitaka Tanaka[1]
Toshiyuki Onoda[2], Kazuyoshi Itai[2], Kozo Tanno[2], Masaki Ohsawa[2]
Kiyomi Sakata[2], Yuki Yoshida[3], Kazuko Kawamura[4], Shiniji Makita[1], Akira Okayama[5]

Department of Internal Medicine (Cardiology Division)[1], Preventive Medicine[2], and Neurosurgery[3], Iwate Medical University, Morioka, Japan; [4]Iwate Health Service Association, Morioka, Japan; [5]The First Anti-tuberculosis Association, Tokyo, Japan

Correspondence Author:
Motoyuki Nakamura, MD
Division of Cardiology,
Department of Internal Medicine and
Memorial Heart Center
Iwate Medical University
19-1 Uchimaru, Morioka, Iwate 020-8505
nkmrmoto@iwate-med.ac.jp

ABSTRACT

Background: Plasma B-type natriuretic peptide (BNP) levels are confounded by renal dysfunction. The aim of this study was to examine whether plasma BNP might be a reliable biomarker for predicting the onset of cardiovascular (CV) events in a population-based cohort with impaired renal function.

Methods and Results: Baseline data, including plasma BNP, serum creatinine, and urinary protein, were determined in participants from a community-based population. Estimated glomerular filtration rate (GFR) was calculated, and chronic kidney disease (CKD) was defined in the following two ways; GFR<60 ml/min/1.73 m^2 and/or proteinuria (CKD definition-1), and GFR<60 ml/min/1.73 m^2 (CKD definition-2). The CV endpoint was surveyed prospectively. The cohorts were followed for 5275 person-years for CKD definition-1, and for 4350 person-years for CKD definition-2. The CV event free survival rate in the highest BNP quartile in either CKD definitions was the lowest among the quartile groups ($p < 0.001$). In multivariate Cox regression models adjusted by traditional cardiovascular risk factors and atrial fibrillation, relative risk (RR) for CV events was significantly higher in the highest BNP quartile compared with the lowest BNP quartile (CKD definition-1, RR=3.51, $p<0.01$: CKD definition-2, RR=4.67, both $p<0.01$).

Conclusions: Measurement of plasma BNP levels provides strong predictive information about the future onset of CV events in CKD subjects selected from the general population.

KEY WORDS; *heart failure/stroke/renal failure/general population*

Chronic kidney disease (CKD) defined by reduced glomerular filtration rate (GFR) and/or proteinuria increases the risk of cardiovascular (CV) disease and end stage renal disease [1]. In population-based studies, the prevalence of CKD has been shown to be 7% in persons aged more than 30 years and to be increased 23-36% in persons aged more than 65 years [2]. The trend in the prevalence of CKD has been speculated to increase over time in line with the recent increasing prevalence of diabetes, obesity, and hypertension [3]. Several reports have emphasized that early identification and treatment of CKD are necessary to prevent serious outcomes in this disorder [1,4]. However, considering the large number of persons with CKD in the general population, it may not be easy to provide pharmacological and non-pharmacological interventions for all stages of CKD. In view of these limitations, it may be practical to select CKD subjects at relatively high risk for CV diseases from the general population, and then provide treatment to prevent the onset of CV diseases. However, there are no established markers to stratify CV risk in CKD subjects with mild renal dysfunction, such as stage 3 CKD, in mass screening settings.

Natriuretic peptide family proteins including B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-pro BNP), are released from the heart in response to increased intracardiac pressure, cardiac pump dysfunction, hypertensive ventricular hypertrophy, and myocardial ischemia. In community-based studies, increased circulating levels of BNP and NT-pro BNP have been reported to relate to a high risk of CV events and mortality [5,6]. The high prevalence of CV events in the group with elevated plasma levels of BNP and NT-proBNP are believed due to the high prevalence of subclinical heart disease in these groups. However, plasma concentrations of BNP and NT-proBNP increased as GFR declined in patients with and without apparent cardiac disorders [7,8]. In view of these facts, it is unclear whether plasma BNP levels might be a reliable biomarker for the prediction of CV

events in the cohort of CKD selected from the community-based population.

CKD is usually defined by two biomarkers of renal function such as urinary protein and reduced GFR. Several community-based studies have applied only the latter definition [9-11]. However, it is uncertain whether the two biomarkers (GFR and urinary protein) provide complementary or overlapping information for CV risk. Cirillo et al. reported that the use of only one of these two biomarkers underscores the potential to misclassify patients as having or lacking CKD, thus misinterpreting the role of CV risk [12]. Therefore, the present study provided two CKD definitions, namely, 1) GFR < 60 ml/min/1.73 m^2 and/or proteinuria; 2) GFR < 60 ml/min/1.73 m^2 , and examined whether plasma BNP might be a reliable biomarker for predicting onset of CV diseases in the CKD cohort selected from the community-based general population.

METHODS

Study Population

The original cohort of the Iwate-KENCO study was recruited from the community-based population living in Ninohe, Kuji, and Miyako districts of northern Iwate prefecture, Japan. The details of the recruitment and measurements of the cohort were shown in previous reports [13,14]. The total number of participants who agreed to join the Iwate-KENCO study in the three districts was 26,469 (original cohort). Of the original cohort living in Ninohe and Kuji districts (n = 15,927), 15,394 subjects (97%) had BNP measurements (BNP cohort: men 5,288; women 10,106).

Subjects were excluded from the present analysis for the following reasons: age under 40 (n = 575); history of cardiovascular events, such as myocardial infarction, stroke, or heart failure

(n = 507); missing data of serum creatinine level (n = 28), body mass index (n = 47), ECG tracing (n = 717), and blood pressure data (n = 4); or estimated GFR < 30 ml/min/1.73 m^2 (n = 28). The final statistical analysis was therefore performed on 13,526 subjects (men 4,542; women 8,984). This study protocol was approved by the university ethics committee and by local institutional review committees. All participants gave written informed consent.

Definition of CKD

The estimated GFR was calculated using an equation from the Modification Diet in Renal Disease Study (MDRD) for the Japanese population [15]. A urine sample was obtained during a multiphasic health examination and urinary protein was semi-quantitatively determined using a dipstick test (Uropaper alpha II, Eiken). Proteinuria was defined as a urine dipstick protein result of trace or more. CKD was defined in the present study in 2 ways; 1) GFR < 60 ml/min/1.73 m^2 and/or proteinuria (CKD definition-1); 2) GFR < 60 ml/min/1.73 m^2 (CKD definition-2).

Measurements

Blood samples were drawn from a peripheral vein in the seated position. When blood samples for routine blood testing were being taken, an additional 2 ml blood sample 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 our laboratory each afternoon. The samples were then centrifuged at 1,500 g for 10 minutes. After separation, plasma samples were stored frozen at –20°C until transportation to the Shionogi central laboratory for assaying (Osaka, Japan). Plasma BNP levels were measured by direct radioimmunoassay using monoclonal antibodies specific for human BNP (Shiono RIA BNP kit, Shionogi).

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. Serum creatinine level was determined by an enzymatic method using an auto-analyzer (Hitachi 7700).

All subjects used a self-reported questionnaire to confirm the medical history including status (yes or no) of prescribed drugs for hypertension, diabetes, hypercholesterolemia, stroke, angina, heart failure and myocardial infarction. Smoking status (current, past smoker, or non-smoker) was also assessed by a questionnaire.

Risk Factor Definitions

Systemic blood pressure was measured by well-trained persons. All subjects were seated for at least 5 minutes before measurement using an automatic device (BP-103i II, model 513000, Nippon Colin). Measurement was performed twice, with the mean value used for statistical analysis. Hypertension was defined as systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg and/or the use of antihypertensive medication. 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 $\geq$ 200 mg/dl and/or HbA1c value $\geq$ 6.5 % and/or use of anti-diabetic agents including insulin. Hypercholesterolemia was defined as a serum concentration $\geq$ 240 mg/dl and/or the use of anti-lipidemic medications.

Outcome

A follow-up survey assessing mortality, migration, and the incidence of heart failure, acute myocardial infarction and sudden death, and stroke was carried out after the baseline study. All deaths and migration were confirmed by the official resident registration data issued by the

local government offices.

Admission cases of heart failure in the cohort were checked by the regional registration survey data, which records primary hospital discharge diagnoses in the study area. The cases of heart failure were objectively defined by the Framingham criteria [16]. Details of this register have been described previously [17]. The event of non-sudden fatal myocardial infarction was also based on the hospital registration survey data. The diagnosis of acute myocardial infarction was based on the Monica study criteria [18]. Sudden cardiac death within one hour after the onset of acute illness was examined using the death records and then checked medical records of the hospitals within the survey areas. Stroke registry was used for the outcome study [19]. Stroke was defined as a sudden onset of focal neurological deficit of >= 24 hours' duration and confirmed by brain computed tomography or magnetic resonance imaging.

Statistical Analysis

Continuous variables are shown as mean +/- SD. CKD subjects were divided into quartiles according to their baseline plasma BNP levels. To compare results among quartiles, ANOVA or chi-square test was used as appropriate. Survival from entry into the study was estimated using the Kaplan-Meier method, followed by a trend test (Log rank). The association between baseline plasma BNP levels and end point CV diseases (new onset of heart failure, acute myocardial infarction/sudden cardiac death, and stroke) was evaluated. Using a Cox proportional hazards regression model, hazard ratios (HRs) for plasma BNP with CV events were assessed. In this multivariable proportional-hazards regression model, adjustments were made for analyses for age, body mass index, and the presence or absence of hypertension, diabetes, hypercholesterolemia, current smoking, and atrial fibrillation. For analyses of CV

incidence, person-years were censored at the date of CV events, the date of emigration from the study area, the date of death, or the end of the follow-up period, whichever came first. All statistical analysis was performed using SPSS software. A significant difference was defined as $p < 0.05$.

RESULTS

As shown in Table 1, the number of cases of CKD definition-1 was 1901 (727 in men, 1174 in women). In this type of CKD, the prevalence within the community-based population was 14% (16% in men, 13% in women). The mean age was 67.9 years old, and the mean GFR was 57.4 ml/min/1.73 m^2. The proteinuria was found in 23% of the subjects. The percentages of cases of hypertension, diabetes, and atrial fibrillation were 54%, 7.5%, and 3.1%, respectively. The median level of plasma BNP was 22.7 pg/ml.

The number of cases of CKD definition-2 was 1578 (552 in men, 1026 in women), and the prevalence was 12% (12% in men, 11% in women) within the community-based population. The percentages of hypertension, diabetes, and proteinuria were 53%, 5.3%, and 6.9%, respectively. The prevalence of atrial fibrillation was 2.9%. The median level of plasma BNP was 23.5 pg/ml in CKD definition-2 cases (Table 1).

The cohorts were followed for 5275 person-years in CKD definition-1, and for 4350 person-years in CKD definition-2, respectively. Composite CV events (heart failure, acute myocardial infarction, sudden cardiac death, stroke) during the follow-up period (mean, 2.8 years) were found 62 cases in the CKD definition-1 group and 43 cases in the CKD definition-2 group. The number of the CV events per 1000 person-years was 11.7 and 9.9 in the CKD definition-1 and the CKD definition-2 groups, respectively.

Kaplan-Meier curves for CV event free rate according to the BNP quartiles in both CKD