Table 2
Descriptive characteristics of 1926 men aged 40–69 years with CRP levels less than 10 mg/L according to quartile groups of CRP levels

CRP levels (mg/L)	0.1–0.2	0.3–0.4	0.5–0.9	1.0–9.4	*P* value
Number	506	471	492	457	
Age (years)	57.4 (8.5)	58.2 (8.2)	58.3 (8.4)	59.6 (8.2)	<0.001
BMI (kg/m^2)	22.8 (2.7)	23.8 (2.6)	24.4 (3.0)	24.5 (3.2)	<0.001
SBP (mm Hg)	123.9 (18.7)	128.5 (19.0)	129.2 (19.6)	130.1 (19.8)	<0.001
Regular drinker	50.0%	49.8%	50.0%	50.1%	0.532
Exercise habit	25.8%	33.4%	34.7%	32.3%	0.022
Current smoker	35.0%	35.9%	42.1%	45.7%	<0.001
TC (mg/dL)	190.9 (30.9)	198.6 (32.1)	202.0 (35.1)	200.5 (36.5)	<0.001
TG (mg/dL)	118.8 (72.6)	141.5 (93.4)	160.7 (112.1)	162.7 (116.6)	<0.001
HDLC (mg/dL)	61.9 (15.0)	58.7 (14.9)	54.0 (13.9)	53.3 (14.9)	<0.001
LDLC (mg/dL)	110.3 (28.3)	117.6 (30.6)	122.8 (31.6)	122.7 (33.5)	<0.001
Plasma glucose (mg/dL)	110.6 (32.6)	114.7 (41.9)	113.5 (36.9)	119.4 (45.5)	0.002
HbA1c (%)	4.95 (0.56)	5.04 (0.75)	5.14 (0.91)	5.27 (0.95)	<0.001

Data are expressed as means (standard deviation) or percentages. *P* values for linear trend tests among quartile groups.
Abbreviations: NS, not significant; TC, total cholesterol level; TG, triglyceride level; HDLC, high-density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; HbA1c, percentage of glycosylated hemoglobin; SBP, systolic blood pressure.

level and between pack-years of smoking and CRP level [6–8,23]. Tracy et al. did not find a dose–response relationship between pack-years of smoking and CRP level [23]. Koenig et al. analyzed the associations between number of cigarettes smoked per day and CRP level and between pack-years of smoking and CRP level, but they did not report a dose–response relationship between number of cigarettes smoked per day and CRP levels or between pack-years of smoking and CRP level [6,7]. Fröhlich et al. reported that the number of cigarettes smoked per day, pack-years of smoking and duration of smoking are positively associated with CRP levels in men, although CRP levels in moderate to heavy smokers (13 cigarettes or more per day) were similar in their study [8].

It has been reported that there is a strong and consistent dose–response relationship of smoking with coronary artery disease (CAD) and that there is a positive relationship between the risk of development of CAD and CRP level [4,7,24]. However, our data did not show a positive association between number of cigarettes smoked per day and CRP level in current smokers. This is in contrast to the dose–response relationship between number of cigarettes smoked per day and HDLC level found in our study (crude mean levels of HDLC: 56.3 mg/dL in mild smokers, 56.1 mg/dL in moderate smokers, 54.4 mg/dL in heavy smokers, linear trend test: $P < 0.05$) and in a previous study [25]. Variation of susceptibility to smoking may explain the lack of a dose–response relationship between CRP level and number of cigarettes smoked. Smokers with high CRP levels possibly have a high risk of development of CVD.

Table 3
Standardized regression coefficient by multiple regression analysis predicting logarithm-transformed CRP among 1926 men aged 40–69 years with CRP levels less than 10 mg/L

	Standardized coefficient	*P* value
Current smoking		
Number of cigarettes		
1–19/day	0.082	0.001
20–29/day	0.096	<0.001
30/day	0.106	<0.001
Ex-smoking	0.059	0.020
Age (years)	0.132	<0.001
BMI (kg/m^2)	0.141	<0.001
SBP (mm Hg)	0.069	0.004
HDLC (mg/dL)	−0.182	<0.001
LDLC (mg/dL)	0.113	<0.001
HbA1c (%)	0.110	<0.001

Abbreviations: BMI, body mass index; HDLC, high-density lipoprotein cholesterol level; LDLC, low-density lipoprotein cholesterol level; HbA1c, percentage of glycosylated hemoglobin; SBP, systolic blood pressure.

In past smokers, our data showed that CRP levels were intermediate between those in non-smokers and those in current smokers. Similar results regarding CRP levels in past smokers were reported [6,8], on the other hand, some studies reported that mean CRP levels in past smokers were similar to those in nonsmokers [7].

As for the relationship between smoking cessation period and CRP levels, Frölich et al. reported that duration of smoking cessation is inversely associated with CRP levels in men. However, CRP levels in past smokers who had not smoked for more than 20 years were still higher than those in subjects who had never smoked [8]. In the present study, it was found that the longer the smoking cessation period was, the lower the CRP levels in past smokers were. Adjusted CRP levels in past smokers who had not smoked for 5 years or more were similar to those in subjects who had never smoked. Our results suggested that the risk reduction of CAD by smoking cessation could be explained by decline of CRP level.

There are several limitations of our study. First, smokers who are in good physical condition can continue to smoke the same number of cigarettes per day, whereas smokers who are not in good condition tend to cease smoking or reduce the number of cigarettes smoked per day. This may possibly explain the lack of a dose–response relationship between CRP level and number of cigarettes smoked per day. Second, some subjects in this study may have quit

Table 4
Non-adjusted and adjusted geometric means of CRP level for various categories of smoking status among 1926 men aged 40–69 years with CRP levels less than 10 mg/L

	Number	CRP (mg/L) geometric mean	Estimated CRP (mg/L)		
			geometric mean	95%CI	
Smoking status					
Non-smoker	661	0.43	0.41	(0.39–0.450)	‡, †
Current smoker	762	0.54	0.57	(0.53–0.61)	‡, †
Past smoker	503	0.49	0.48	(0.44–0.52)	†
Current smoker groups					
Number of cigarettes/day*					
1–19 /day	217	0.52	0.55	(0.48–0.62)	Linear trend NS
20–29 /day	371	0.54	0.56	(0.51–0.62)	
30 /day	172	0.58	0.62	(0.53–0.71)	
Pack-years of smoking**					
0.3–25.0 years	257	0.49	0.53	(0.46–0.59)	Linear trend NS
25.2–39.0 years	229	0.51	0.57	(0.50–0.64)	
40.0–105.0 years	273	0.45	0.61	(0.54–0.68)	
Past smoker groups***					
Length of cessation period					
<5 years	119	0.61	0.58	(0.49–0.70)	†
5 years	354	0.47	0.45	(0.41–0.50)	†

Estimated CRP levels for persons aged 58.4 years with BMI of 23.9 (kg/m^2), SBP of 127.8 (mm Hg), HDLC of 57.0 (mg/L), LDLC of 118.2 (mg/L), and HbA1c of 5.10 (%). 95% CI (confidence interval) is based on standard errors from analysis of covariance.
‡ $P < 0.05$ by multiple comparisons (Bonferroni's method).
†† $P < 0.01$ by multiple comparisons (Bonferroni's method).
* Numbers of cigarettes smoked per day were unknown in two current smokers.
** Somoking duration was unknown in one current smoker.
*** Cessation periods were unknown in 30 past smokers.

smoking because of poor physical condition. Third, since past smokers who had not smoked for more than 5 years had a rather short smoking history and short smoking exposure period, the likelihood of smoking-related inflammation seems to low in those subjects. These factors may have accentuated the difference between CRP levels in the short cessation group and long cessation group. Finally, it is necessary to test in a longitudinal prospective investigation whether current smokers with high CRP levels have a high risk of developing CVD and whether CRP levels recover to former levels after smoking cessation.

In conclusion, CRP levels in current smokers are elevated but unrelated to the number of cigarettes smoked per day. The longer the smoking cessation period is, the lower are CRP levels in past smokers. The reduction in risk of development of CVD can be partially explained by decline of CRP level due to smoking cessation.

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Plasma B-type Natriuretic Peptide Levels and Risk Factors for Congestive Heart Failure in a Japanese General Population

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SUMMARY

This cross-sectional study was performed to establish the rationale for BNP testing for identifying subjects at high risk of congestive heart failure (CHF) in a screening setting.

Plasma BNP concentrations were measured in 8,178 community-dwelling residents (mean age, 62 ± 12 years; 3,194 males). First, in order to determine age- and sex-related reference values for plasma BNP levels, subjects having factors known to influence plasma BNP levels were excluded. The remaining 3,410 subjects were eligible for the reference study. Second, to verify BNP testing for screening for subjects at high risk of CHF, the clinical characteristics of subjects showing abnormally high plasma BNP levels (≧ 97.5 percentile for each age- and sex-specific value of the reference cohort) were examined.

In the reference subjects, plasma BNP levels increased with age in both genders, and were higher in women than in men. In the original cohort, age- and sex-specific reference values for high plasma BNP levels were related to the presence of major ECG abnormalities, hypertension, mildly elevated serum creatinine levels, and a history of coronary heart disease.

The results of the present study indicate that individuals with high plasma BNP levels in the community have accumulating risk factors for CHF. This suggests that plasma BNP measurement may be a useful screening test for identification of individuals at high risk of CHF within a Japanese general population. (Int Heart J 2005; 46: 465-475)

Key words: Brain natriuretic peptide, Congestive heart failure, Screening test

THE prevalence of congestive heart failure (CHF) is growing with an increase in the mean age of the population. Once overtly manifest, CHF is an extremely lethal condition associated with a very poor quality of life and prognosis. The

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mortality rate after the onset of CHF remains high despite recent advances in the management of this condition.[1] Because most patients with CHF have several modifiable risk factors,[2] it is important to target its preclinical stages and treat known risk factors before the development of overt CHF. It is therefore essential that a screening test be established to identify individuals at high risk of CHF early enough to prevent or postpone progression to overt CHF.[3]

B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the myocardium in response to changes in intracardiac volume and pressure.[4,5] Plasma BNP levels are known to be elevated in patients with symptomatic left ventricular systolic dysfunction[6,7] and correlate to New York Heart Association (NYHA) class as well as prognosis.[8,9] In addition, irrespective of the degree of left ventricular dysfunction, plasma BNP levels have been shown to be elevated in patients with various cardiac disorders including previous myocardial infarction, cardiomyopathy, valvular heart disease, hypertensive heart disease, and atrial fibrillation.[6,10-13] It is therefore possible that measurement of plasma BNP levels might be a potential screening marker for identifying individuals with asymptomatic CHF as well as those at high risk of CHF due to various forms of structural heart disease.[14,15]

These suggest that plasma BNP levels might be elevated in subjects with precursors of CHF and thus may serve as a useful predictor for new onset of CHF in a screening setting in the general population. However, in the general population, recent reports have shown that the plasma BNP level is affected by extracardiac factors such as estrogen,[16] obesity,[17] and genetics.[18] In fact, median plasma BNP levels in healthy subjects are clearly higher in women than men.[16,19] This may contradict epidemiological evidence indicating a higher prevalence of cardiovascular disorders in men. These observations suggest that plasma BNP measurement might not be an optimal marker with which to identify subjects at high-risk of CHF in mass-screening. Although only one report, the Framingham study, has shown that a subject group with plasma BNP levels in the highest third of the range measured exhibited an incidence of CHF several times higher than that in the lowest group,[20] no studies have demonstrated whether plasma BNP is a sensitive marker for subjects at high-risk of CHF and thus a predictor of new onset CHF in the Japanese general population.

The objective of this cross-sectional study was to validate the hypothesis that a high plasma BNP level is a useful marker of individuals at high risk of CHF within the Japanese general population.

METHODS

Study population: The Iwate-Kenpoku Cohort (Iwate KENCO) study was designed to prospectively investigate the risks of CHF, acute myocardial infarction, and stroke in a general adult population in northern Japan.[21] The sample for the present investigation consisted of 8,178 participants (male; 2,906: female; 5,272) who participated in this cohort study between April and December 2002. All participants gave written informed consent. The study protocol was approved by the Ethics Committee of Iwate Medical University.

Baseline measurements: In the baseline examination, all participants underwent routine anthropometrical measurement, an ECG, blood pressure measurement, and laboratory assessment of cardiovascular risk factors including plasma BNP levels. In addition, a self-administered questionnaire was used to ascertain family history, symptoms, smoking habits, and medical history including the status of drugs prescribed for hypertension, diabetes, hypercholesterolemia, stroke, angina, CHF, and myocardial infarction. Systolic and diastolic blood pressures were determined with an automatic device placed on the right arm of seated subjects who had rested in a sitting position for at least 5 minutes before measurement. The average of 2 such readings was used for statistical analysis. Hypertension was defined as systolic blood pressure $\geqq$ 140 mmHg and/or diastolic blood pressure $\geqq$ 90 mmHg, and/or use of antihypertensive medication. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Obesity was defined as a BMI $\geqq$ 25 kg/m^2. Diabetes was ascertained either by patient self-reporting or the presence of a nonfasting glucose concentration $\geqq$ 200 mg/dL or HbA1c value $\geqq$ 6.5%. Renal dysfunction was defined as a serum creatinine level $\geqq$ 1.2 mg/dL.

Plasma BNP measurement: Venous blood samples were drawn from the antecubital vein with the participant resting in a seated position. The samples were collected into ethylenediaminetetraacetic acid (EDTA) tubes. These tubes were stored immediately in an icebox and transported to the central laboratory within 6 hours after collection, and centrifuged at 1,500 g for 10 minutes. After separation, the plasma was stored at -20°C before being assayed for BNP. A noncompetitive immunoradiometric assay based on a 2-site sandwich antibody system (Shionogi & Co., Ltd.) was used to measure BNP levels. The intraassay and interassay coefficients of variation were 5% and 6%, respectively. The lower detection limit of the assay was 0.05 pg/mL.

Reference group: In order to demonstrate the distribution of plasma BNP levels among subjects without evident cardiovascular disease, participants were excluded for the following reasons: any type of ECG abnormality, including major and minor findings,[22] hypertension (see above), history of coronary heart disease (myocardial infarction and/or angina pectoris), diabetes mellitus (see

above), renal dysfunction (see above), and cardiovascular symptoms such as dyspnea on effort, chest pain, chest discomfort, palpitations, and edema. After exclusion of these subjects, a subgroup of 3,410 subjects (mean age, 57 years; 1,056 men and 2,354 women) remained and these were defined as "healthy subjects".

Abnormal BNP and risk factors: Subjects whose plasma BNP levels were greater than the 97.5 percentile point based on the reference group BNP distribution were designated as the "high BNP" group. To examine the relationship between high plasma BNP levels and several clinical characteristics, univariate and multivariate logistic regression analyses were used in the original cohort (n = 8,178). In addition, to elucidate whether this relationship was identical or not in the elderly population, a similar analysis was performed after exclusion of subjects under 65 years of age.

Statistical analysis: Data are presented as the mean ± SD. Differences between groups were determined by one-way ANOVA or χ^2 analysis when appropriate. Plasma BNP was logarithmically transformed for statistical analysis. SPSS software (Chicago, Illinois, USA) was used for statistical analysis. A significant difference was defined as $P < 0.05$.

RESULTS

All participants: Plasma BNP levels were found to range widely, with a distribution skewed towards lower levels (data not shown). The minimum value was less than 0.05 pg/mL in both genders, and the maximum values were 1,280 pg/mL in males and 510 pg/mL in females. A small proportion of subjects (8.7% of males and 6.0% of females) had BNP levels below the limit of detection.

Table I presents the coefficients of correlation in simple linear regression analysis between plasma BNP levels and several clinical variables for all participants. The variable related most significantly to plasma BNP level was age in both genders.

Healthy subjects: The clinical characteristics of 3,410 healthy subjects (1,056 males and 2,354 females; age, 56.7 ± 11.6 years) are described in Table II. The median value of plasma BNP was 7.6 pg/mL in males and 12.1 pg/mL in females. The median plasma BNP level increased with age in both genders, and was higher in females across all age groups. The 97.5 percentile of BNP levels in the four 10-year age groups (40-49, 50-59, 60-69, and 70-79) were 26.3, 37.2, 64.9, and 72.4 pg/mL in males, and 40.5, 44.5, 61.8, and 77.0 pg/mL in females, respectively.

Factors contributing to high BNP levels: Subjects with plasma BNP levels ≧ 97.5 percentile of the gender-age referenced level were designated as the high BNP group (n = 704). Using univariate logistic regression analysis, we tested the associations between each clinical parameter and the high BNP group to evaluate

Table I. Correlation Among Log BNP and Other Clinical Variables in all Subjects

Variable	Males (n = 2,906)	Females (n = 5,272)
Age (years)	0.42**	0.31**
Systolic BP (mmHg)	0.11**	0.13**
Heart rate (bpm)	-0.19**	-0.15**
Pulse pressure (mmHg)	0.17**	0.15**
Body mass index (kg/m^2)	-0.06**	-0.03*
Hemoglobin (g/dL)	-0.20**	-0.08**
Total protein (mg/dL)	-0.11**	-0.08**
Serum creatinine (mg/dL)	0.08**	0.12**
Total cholesterol (mg/dL)	-0.14**	-0.02*

*$P < 0.05$, **$P < 0.01$

Table II. Mean Values of Several Clinical Characteristics in Reference Subjects

Characteristic	Males (n = 1,056)	Females (n = 2,354)
Age (years)	57.2 ± 13	56.7 ± 11
Body mass index (kg/m^2)	23.3 ± 2.7	23.3 ± 3.0
Systolic BP (mmHg)	117 ± 12	113 ± 13
Diastolic BP (mmHg)	71 ± 8	67 ± 8
Heart rate (bpm)	71 ± 10	73 ± 10
Serum creatinine (mg/dL)	0.80 ± 0.12	0.62 ± 0.10
Total cholesterol (mg/dL)	196 ± 34	205 ± 33
BNP (median: pg/mL)	7.6	12.1

clinical factors contributing to high plasma BNP levels (Table III). In both genders, hypertension, major ECG abnormalities, and mildly elevated serum creatinine levels were associated with high BNP levels (all, $P < 0.05$). The correlation between high plasma BNP and history of coronary heart disease was evident only in men ($P < 0.05$). Multivariate logistic regression analysis was performed to examine independent clinical factors contributing to high BNP levels (Figure 1). In males, hypertension ($P < 0.01$), major ECG abnormalities[21] ($P < 0.01$), history of coronary heart disease ($P < 0.01$), and mildly impaired renal function ($P < 0.05$) were independently associated with high BNP levels. Apart from the history of coronary heart disease, similar trends were found among females (hypertension, $P < 0.01$; major ECG abnormalities, $P < 0.01$; mildly impaired renal function, $P < 0.01$). No correlation was found between obesity and high plasma BNP levels in either gender.

Table III. Univariate Logistic Regression Analysis of the Relationship Between Clinical Parameters and High BNP Levels

	Males	Females
	Odds ratio (95% CI)	Odds ratio (95% CI)
Hypertension	1.85 (1.42-2.42)*	2.26 (1.87-2.72)*
ECG abnormalities	8.55 (5.62-13.0)*	4.31 (2.77-6.70)*
History of CHD	3.24 (1.79-5.83)*	2.04 (0.99-4.20)
CRE ≧ 1.2 mg/dL	2.59 (1.43-4.55)*	5.59 (2.35-13.2)*
Diabetes	1.02 (0.61-1.68)	1.34 (0.89-2.03)
Obesity	1.02 (0.77-1.35)	1.02 (0.84-1.24)
Smoking	0.89 (0.68-1.17)	0.56 (0.30-1.04)

*$P < 0.05$

CHD = coronary heart disease; CRE = serum creatinine.

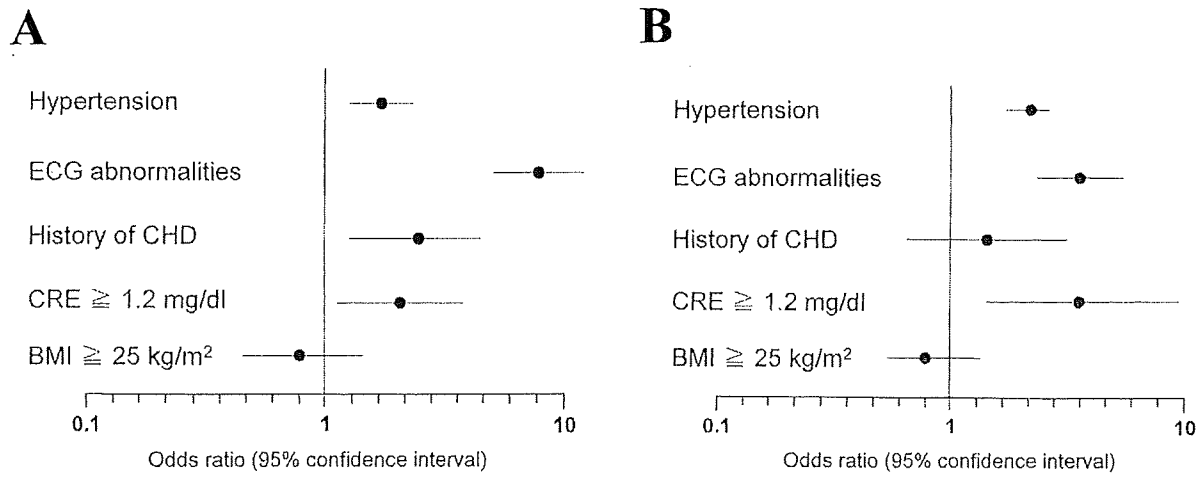

Figure 1. Multiple logistic regression analysis of independent determinants of high plasma BNP levels in males (**A**) and females (**B**). CHD = coronary heart disease; CRE = serum creatinine.

Age greater than 65 years: We also tested independent clinical parameters contributing to high BNP levels in elderly participants (age ≧ 65). Abnormally high plasma BNP levels (≧ 97.5 percentile of the age-sex referenced level) in healthy elderly subjects were almost the same in both genders (males, 74.0 pg/mL, females, 74.2 pg/mL). We therefore used 74 pg/mL as the cut-off level for abnormally high plasma BNP in elderly subjects. Using multivariate logistic regression, we found that major ECG abnormalities (odds ratio, 7.0; 95% CI, 4.17-11.8; $P < 0.01$), history of coronary heart disease (odds ratio, 2.0; 95% CI, 1.02-4.05; $P < 0.05$), mildly impaired renal function (odds ratio, 1.9; 95% CI, 1.01-3.78; $P < 0.05$), and hypertension (odds ratio, 1.6; 95% CI, 1.15-2.28; $P < 0.01$) were also independently associated with high BNP levels in elderly males. In females, high

Figure 2. Median plasma BNP levels and number of heart failure risk factors.

serum creatinine (odds ratio, 5.3; 95% CI, 1.89-15.1; $P < 0.01$), major ECG abnormalities[21] (odds ratio, 4.7; 95% CI, 2.74-8.24; $P < 0.01$), and hypertension (odds ratio, 1.5; 95% CI, 1.15-2.28; $P < 0.01$) were independently correlated with high BNP levels.

Number of CHF risk factors and BNP: Figure 2 shows the relationship between median plasma BNP levels and the number of risk factors contributing to CHF by gender. Risk factors for CHF were assumed to include advanced age (≧ 65 years), hypertension, history of coronary heart disease, mildly elevated serum creatinine level, major ECG abnormalities, smoking history, diabetes mellitus, and obesity. The median plasma BNP level in males was 6.7 pg/mL with no CHF risk factors and 33 pg/mL with five or more risk factors. In females, as in males, the accumulation of risk factors increased plasma BNP levels from 12 pg/mL with no risk factors to 28 pg/mL in the group with multiple risk factors.

DISCUSSION

To the best of our knowledge, this is the first study to provide cross-sectional data in relation to CHF risk factors and plasma BNP levels in a Japanese community-based population. The main findings of our study can be summarized as follows. First, median plasma BNP levels in a healthy population increase with age and are higher in women. Second, in the adult general population, major ECG abnormalities, hypertension, history of coronary heart disease, and mildly ele-

vated serum creatinine were significant independent variables associated with age- and sex-specific high plasma BNP levels. Third, median plasma BNP levels increase in proportion with the number of established CHF risk factors. The present study therefore demonstrated that, in a general population, subjects with age- and sex-specific reference values for high plasma BNP levels are likely to be at high risk of CHF.

Importance of identification of CHF high-risk subjects: Previous reports have suggested that plasma natriuretic peptide measurement is useful for identifying patients with left ventricular systolic dysfunction within a general population[23,24] and for predicting patients with reduced left ventricular function from among high-risk patients.[25] In addition, plasma natriuretic peptide testing has been reported to have high sensitivity and specificity for the identification of true CHF among patients suspected of having CHF in a primary setting.[26] These observations indicate that plasma BNP measurement may be a helpful aid in the diagnosis of CHF. However, no information is available concerning the utility of plasma natriuretic peptide measurements for screening subjects at high risk for CHF in the Japanese general population.

Since there is a growing clinical interest in subjects at high risk of CHF, as evidenced by its inclusion in a new staging system for CHF,[27] it would seem important to establish a new method for screening subjects with accumulating CHF risk factors or with asymptomatic structural heart disease [stage B in the 2001 ACC/AHA guidelines for CHF[27]] from within large populations. In fact, several reports have shown that effective treatment of hypertension decreases left ventricular hypertrophy, which is known to be a risk factor for CHF.[28,29] The treatment of asymptomatic patients with diabetes or vascular disease using angiotensin-converting enzyme inhibitors has yielded significant reductions in the prevalence of CHF.[30,31] Given these considerations, it is important to identify CHF high-risk subjects with asymptomatic structural heart disease who will be prone to develop overt CHF. The present study is the first to demonstrate a relationship between plasma BNP levels and CHF risk factors in the general population, and to suggest that in a screening setting age-and sex-specific referenced high plasma BNP levels may serve as a marker for subjects with an accumulating risk of CHF.

Age-gender and plasma BNP levels: Among healthy subjects, plasma BNP levels increase with age and are higher in women than in men. Similar trends have been observed previously.[16,18] These findings suggest that we should include consideration of the effects of age and gender in the interpretation of plasma BNP results. There are several possible explanations for the observed difference in median plasma BNP levels between genders. In healthy subjects, median plasma BNP values were higher in women in all age groups. Redfield, *et al* reported that there

was a relationship between hormone replacement therapy and increased plasma BNP levels in women,[16] suggesting an influence of estrogen. Other investigators have reported that women had significantly higher left ventricular end-systolic elastance and lower passive diastolic compliance compared with age-adjusted men.[32,33] These left ventricular biomechanical characteristics in women may stimulate BNP production from the heart,[34] giving rise to the difference in plasma BNP levels between the sexes.

Clinical implications: Echocardiography may be one of the most important techniques for screening for asymptomatic structural heart disease with high CHF risk. However, given the cost and resources necessary to implement standard echocardiographic screening in the general population, it would not be practical to employ this technology. If a reliable biomarker could be established, early intervention would become possible. This would make it possible to limit the progression to overt CHF, resulting in a significant improvement in outcomes for CHF. Plasma BNP measurement is relatively inexpensive and BNP can easily be assayed without radioisotope labeling. In addition, plasma BNP has been reported to be relatively stable after storage at room temperature for several hours.[35] It follows, therefore, that plasma BNP testing may be a candidate biomarker for screening for subjects at high risk of CHF.

Limitations: The present study may have failed to detect some subjects with asymptomatic cardiac disorders as echocardiography was not performed in the baseline examination, and the reference values might be biased. However, to obtain the reference level we carefully excluded participants with hypertension, any type of ECG abnormality, previous myocardial infarction, mildly impaired renal function, cardiovascular medications, and cardiac symptoms. It therefore seems unlikely that this bias may have significantly affected our findings.

Because our population was a sample from a multiphasic health checkup, the data presented here need to be interpreted with some caution due to selection bias. However, the present study covered more than 20% of the age-matched population in the area. Moreover, there were very few differences in the frequency of hypertension and history of stroke, and in the distribution of plasma total cholesterol, random blood glucose levels, and body mass index between this cohort and data from a recent national health survey conducted in a randomly selected adult population.[36] These findings suggest that the selection bias in our study may have been limited. We could not find any association between high plasma BNP levels and history of coronary heart disease in females. This may be explained by the small number of female subjects having a history of coronary heart disease (females: 1.0%, males: 2.4%), especially myocardial infarction. This would mean that the statistical power to detect a significant association in this context may have been limited.

In conclusion, this community-based study has demonstrated that age- and sex-specific reference values for high plasma BNP levels indicate an accumulation of CHF risk factors. This suggests that plasma BNP measurement may be a useful screening test for identifying individuals at high risk of CHF within a Japanese general population.

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総　説

岩手県北コホート研究の登録時横断解析結果ならびに初期追跡調査結果
—介護認定、脳卒中発症登録に着目した解析結果—

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要　約

岩手県北地域コホート研究は，日本人壮年期の早世の要因である循環器疾患を未然に防ぐため，日本人特有のリスク要因について解明し，最終的には日本人の循環器疾患予防のための対策をたてることを主要な目的としている。また高齢者の健康対策に必要な資料を提供することも目的のひとつである。

本研究は平成14年に二戸地域で登録作業が始まり，平成16年久慈地域で登録作業を終了した。18市町村で登録作業を行い，健康診査を受診した総数31,318人（男11,003人，女20,315人）のうち，研究参加の同意が得られたのは26,472名（男9,162名，女17,310名，同意取得率84.5％）であった。

岩手県北部地域の成人26,742名の参加者の登録時検査データの横断解析を行い，血圧値，血清脂質値，糖尿病者割合，高脂血症者割合，肥満者の割合，喫煙率，飲酒習慣，運動習慣，栄養摂取状況を性別・年齢階級別に明らかにした。その結果，高脂血症は，男性では全ての年代で30％前後みられること，女性では40歳未満では10%未満であるの対して50歳以降では40％を超えることが判明した。糖尿病有病率は年齢が上がるとともに上昇し，男性の60代8.4％，70代で9.1％であった。女性では，それぞれ4.3％，5.9％であった。高度肥満者（BMI≧30kg/m^2）割合は，男女ともに20代が最も高かった。新しい循環器疾患予見因子として注目される，高感度CRP値，血漿BNP値，尿中微量アルブミン値についても性年齢階級別にその平均値を明らかにした。

登録調査から平均3.5年の観察期間の追跡調査を行った二戸地域の参加者に関して，総死亡率，脳卒中罹患率ならびに新規介護認定者（要支援または要介護１以上の者）の割合を明らかにした。

脳卒中罹患率は，高齢化が進んだことで過去の報告に比べ高くなっていた。昭和60年の日本人基準人口で年齢調整をすると，従来の報告とほぼ同じ値であった。

これらのイベントに影響する要因についてCox比例ハザードモデルを用いて検討し，脳卒中発症に影響するリスク要因，新規介護認定に影響するリスク要因について明らかにした。脳卒中罹患に関しては，収縮期血圧が高いほど罹患率が高かった。新規介護認定のリスク要因についての検討結果では，脳卒中と同様に収縮期血圧が高いほど介護認定リスクが高かった。高血圧以外の古典的危険因子についてみると，男性では常用飲酒者や禁酒者で介護認定リスクが高くなっていた。女性では，血清総コレステロール値が低いほど，BMIが大きいほど介護認定リスクが高かった。

横断解析では，県北地域全ての住民の基本属性が明らかにされたが，追跡調査は，二戸地域の参加者のみを対象としており，しかもまだ4年未満の追跡期間によって得られたデータをもとにしていることから，リスク要因の検討については十分とはいえない。今後追跡調査対象地域の拡大，追跡調査期間の延長により，循環器疾患発症や介護認定のリスク要因について新しい知見が得られることが期待される。

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緒　言

岩手県北コホート研究は，日本人を対象とした地域ベースのコホート研究である。その主要な目的は，壮年期の早世の要因である心筋梗塞や脳卒中を未然に防ぐため，リスク要因を同定し，薬物治療や，生活習慣への介入によってmodifiable risk factor（遺伝体質とは違って変えることができる要因）を改善して，発症を防ぐという予防医学的なアプローチに沿ったものである。古典的なリスク要因の中でも日本人では十分に関連が明らかにされていない要因，例えば，女性の高脂血症が循環器疾患の発症や死亡に影響しているかどうかは十分に解明されていないことであり，本研究では，日本人では十分に解明されていないリスク要因について，あるいは，日本人特有のリスク要因について解明し，最終的には日本人の循環器疾患予防のための対策をたてることを主要な目的としている。

一方で，日本も含めた先進国の多くは長寿社会が定着し，人口の多くを占める高齢者に対しての対策が重要となってきた[1)]。特に，高齢者ではdisability（身体障害）と寝たきりの問題が大きく，医療的社会的負担が重くのしかかってきている。この負担を減らすには，身体障害や寝たきりに大きく影響する要因を解析し，高齢者の身体障害に大きく影響すると指摘されてきた脳卒中や心不全などの循環器疾患の身体障害への影響度を把握し，そして，高齢者での循環器疾患発症予防についての対策をたてることが急務となっている[1)]。したがって，現在の公衆衛生学では，従来の予防医学が重視してきた，働き盛りの早世を防ぐことを主眼とした青壮年を対象としたリスク要因の同定ならびにリスク要因対策のみでは不十分であり，さらに高齢者の健康対策にも同じような努力を傾ける必要が生じてきたのである。

壮年者で明らかにされた古典的危険因子が高齢者に同じように適応できるかどうかについては十分に明らかにはされていない。古典的危険因子に対する対策とともに，新しい予見因子（CRP，BNP尿中微量アルブミン）についても，壮年者では疾患発症との関連について明らかにされているものの，高齢者に関しては，その正常値や危険と判断されるカットオフポイントさえ定まっていないのが現状である[2)]。

また，日本では，平成12年から介護保険制度を実施してきた。疾病の後遺症や加齢の変化に伴う体力低下と日常生活動作への支障，認知症による生活への支障に対して，医療保険ではなく，介護保険給付により障害を持つ高齢者の支援を目指したものである。高齢者の医療費と同様に，介護保険にかかわる負担も年々増加し，高齢の障害者が増加することを極力抑えて，新たな介護認定登録者をなるべく抑制する必要性が生じてきた。いわゆる介護予防の問題が大きく取り上げられるようになったのである[3)]。

このような時代背景にあって，岩手県北コホート研究は，青壮年を対象とした予防医学的観点のみならず，高齢者を対象とした公衆衛生上の問題点についても着目し，解決のための施策を講ずるための基礎的資料を提供する責任を負っているといっても過言ではない。岩手県北コホート研究は，平成17年度から2年間に渡って，厚生労働省科学研究費補助金（長寿科学総合研究事業，脳卒中危険因子・発症・要介護・医療費に関する大規模縦断研究，主任研究者　小川彰）を受け，主に脳卒中と介護予防に関連した基礎的資料作成のために，岩手県北コホート地域での脳卒中発症登録事業への資金的援助と精度管理及び介護保険認定者調査を実施し，その調査結果を県北コホート参加者のデータベースとリンクさせることで新たな知見を得た。本論文では，登録時の横断解析結果について報告するとともに，登録から4年を経過した時点での二戸地域の追跡調査の結果を，主に脳卒中発症と介護認定について解析した結果を報告する。

対象と方法

対　象

岩手県北コホート研究は，岩手県北部に位置する3保健医療圏（二戸保健医療圏，久慈保健医療圏，宮古保健医療圏）の一般住民を対象としたコ

ホート研究である（図1参照）。各市町村が1年毎に行っている健康診査に参加した住民を対象として，研究の概要説明を行い，研究参加に同意の得られた者を対象に，一般健康診査とは別に，生活習慣問診，栄養調査，追加検査（血漿HbA1c測定，血清高感度CRP測定，血漿BNP測定，尿中アルブミン測定）を行った。

平成14年度から3年間をかけて18市町村で登録作業を行い，健康診査を受診した総数31,318人（男11,003人，女20,315人）のうち，研究参加の同意が得られたのは26,472名（男9,162名，女17,310名，同意取得率84.5%）であった。尚，岩手県北コホート研究では，すべての研究参加者からインフォームドコンセントを取得し，研究内容については，岩手医科大学倫理委員会の倫理審査承認を得て，ヘルシンキ宣言のガイドラインに則って行われた。

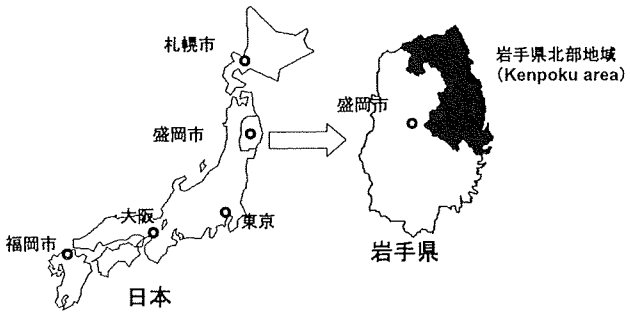

図1．研究対象地域

登録時調査

登録時調査は，市町村の行っている一般健康診査項目（血液検査，身長測定，体重測定，血圧測定）とそれに付け加えて本研究参加者に行われた生活習慣問診と栄養調査ならびに血液・尿検査追加調査項目（血漿HbA1c測定，血清高感度CRP測定，血漿BNP測定，尿中アルブミン測定）からなる。

身長はタニタのデジタル身長測定計（TANITA digital scale Model BWB-200）を用いて測定した。体重はヤガミ社製のデジタル体重計（YAGAMI model 48525YG-200D）を用いて測定した。血圧は，排尿後最低5分間の座位安静を行わせた後2回測定し，2回の計測値の平均値を測定値とした。血圧計は日本コーリン社製（BP-103i Ⅱ Model 513000, Nippon Colin, Komaki, Japan）を用いた。Body mass index（BMI）は体重（kg）を身長（m）の2乗で除して求めた。

安静時12誘導心電図は日本光電社製心電計（FCP-140またはFCP-145）を用いて記録し，心電図判読は1名の検査技師が岩手県予防医学協会の心電図コードに従ってコーディングし，さらに判読結果を1名の医師が再チェックをして確認した。本稿では，循環器疾患発症リスクとして重要である心房細動の有病率を取り上げた。

生活習慣問診は，自記式の問診調査票を用いて行った。問診項目の主な内容は，心疾患既往，脳卒中既往，内服薬服用の有無，飲酒歴，喫煙歴，学校教育期間，婚姻の有無，同居人の有無などである。栄養調査は自記式の食物摂取頻度調査票（日本動脈硬化縦断研究で示されたBDHQ1_1の調査票）を用いた。この栄養調査票は4ページからなり，3つの主要部分からなる。すなわち，食事摂取行動内容と調理法，5種類のアルコール飲料の摂取量と摂取頻度，そして，50品目の主要な食品と非アルコール性飲料の摂取頻度について問う部分からなる。この簡略型の栄養調査票は，16ページからなる栄養調査票を基に作成されたものである。栄養摂取量算出は，日本人栄養摂取量の標準に基づいたコンピュータアルゴリズムを用いて行われた。佐々木による精度管理調査によると，男女各92人での総カロリー摂取量に関しての相関係数は，男0.26，女0.24，コレステロール摂取量に関しては男0.34，女0.33，脂質摂取量に関しては男0.55，女0.60，飽和脂肪酸摂取量に関しては男0.50，女0.57であった。長鎖不飽和脂肪酸摂取量（EPA+DHA）に関しても，男91人で0.37，女91人で0.31の相関係数が得られ，精度管理調査についてはまずまずの成績が得られている（2004年佐々木による検討，未公表データ）。

採血は，非空腹時に行い（随時採血），被験者を座位にさせて，正肘静脈から行った。血液検体は，同日中に解析センター（岩手県予防医学協会）

に搬送して解析した。各種採血項目と測定法ならびに測定機器については表１に示すとおりである。尚，総コレステロール値とHDLコレステロール値測定に関しては，アメリカCDCの精度管理に基づき，大阪府立成人病医療センターによる精度管理を実施している。

本研究では，新しい循環器疾患予見マーカとして注目されている３つの項目を追加項目として取り上げている。ひとつは，高感度CRP測定である。高感度CRP測定は全参加者26,472名中25,928名で実施された。測定原理は免疫比濁法であり，測定機器としてDade Behring社製のネフェロメータⅡを用いた。最低感度は0.05mg/Lであるが，本研究では0.1mg/Lを検出限界とし，0.1mg/L未満の測定値は0.1mg/Lとみなして解析した[4]。

２番目の項目は血漿BNP濃度である。本検査項目は26,472名中17,365名で測定実施された。ヒトBNPに対するモノクローナル抗体を用いた直接免疫アッセイ法（Shiono RIA BNP kit, Shionogi & Co., Ltd., Japan）により測定した。測定手技内または測定手技間での変異相関係数はそれぞれ５％と６％であり，測定法精度管理は十分に保たれていることが実証されている[5]。

３番目の追加項目は，尿中アルブミン測定である。本項目測定は26,472名中25,716名で実施された。随時採取された尿サンプルは採取当日中に岩手県予防医学協会に搬送し，同日解析した。解析原理は免疫比濁法であり，Dade Behring社製のネフェロメータを用いた高感度測定を行った。尚，同時に尿中クレアチニン濃度を酵素比色定量法により測定し，尿中アルブミン24時間定量値の代用である尿中アルブミン指数（The urine albumin-creatinine ratio（UACR））を求めた。尿中アルブミン量測定限界は６mg/lであり，測定間誤差は５％以内であった[6]。

登録時属性分析と用語定義

本研究参加者の年齢分布は18歳から95歳までであった。性別・年齢階級別の参加者属性を見る目的で10歳階級で各検査項目の平均値（標準偏差）と頻度（％で表記）を表記した。人数が少ない10代参加者は20代参加者のグループに含め，90代参加者は80代参加者のグループに含めて解析をした。高血圧は，収縮期血圧が140mmHg以上または拡

表１．検査項目ならびに測定方法

項目	単位	基準範囲	測定方法	分析機器
血液生化学				
AST	U/L	0-39	JSCC標準化対応法	日立7700
ALT	U/L	0-39	JSCC標準化対応法	日立7700
γGTP	U/L	0-74/0-49	JSCC標準化対応法	日立7700
ALP	U/L	120-389	JSCC標準化対応法	日立7700
CHE	U/L	100-239	7	日立7700
T-bil	mg/dL	0.2-1.1	酵素法	日立7700
TP	g/dL	6.4-8.2	ビューレット法	日立7700
Alb	g/dL	4.0-5.1	BCG法	日立7700
Cre	mg/dL	0.5-1.0/0.3-0.7	酵素法	日立7700
UA	mg/dL	4.0-7.5/2.7-5.4	ウリカーゼ・ペルオキシダーゼ法	日立7700
TC	mg/dL	130-219	酵素法	日立7700
TG	mg/dL	40-239**	酵素比色法	日立7700
HDLC	mg/dL	40-99	第一化学コレステストN HDL	日立7700
LDLC	mg/dL	0-139	第一化学	日立7700
血糖値	mg/dL	60-139**	ヘキソキナーゼUV法	日立7700
HbA_{1c}	%	4.0-5.4	HPLC法	トーソーHJC-723G7
血球数測定				
RBC	$\times 10^4/\mu L$	400-579/350-549	シースフローDC検出法	シスメックス SE-900
Hb	mg/dL	13.6-17.9/12.0-16.9	SLSヘモグロビン法	シスメックス SE-900
Ht	mg/dL	41.0-53.9/36.0-51.9	赤血球パルス波高値検出法	シスメックス SE-900
その他のバイオマーカー				
hsCRP	mg/L		免疫比濁法	Dade Behring Immmunonephelometer Ⅱ
BNP	pg/mL		直接免疫アッセイ法	ShionoRIA BNP kit
尿アルブミン	mg/L		免疫比濁法	Dade Behring Immmunonephelometer Ⅱ

張期血圧90mmHg以上または降圧薬内服中の者と定義した。糖尿病は，随時血糖値が200mg/dL以上またはHbA1c値が6.5％以上または糖尿病薬を内服中の者と定義した。高脂血症は，血清総コレステロール値が220mg/dL以上，またはHDLコレステロール値が40mg/dL未満または高脂血症薬服用中の者とした。随時採血であることから，定義項目に中性脂肪値は含めなかった。常用飲酒者は週5日以上飲酒している者，機会飲酒者は現在の飲酒習慣を持ち，かつ，週5日未満の飲酒者と定義した。運動習慣は，1回60分以上の運動を月に8回以上行っていることと定義した。肥満者は，BMIが25以上の者を軽度肥満者，BMIが30以上の者を高度肥満者と定義した。

高感度CRPの解析にあたり，10mg/L以上の値を示した者は，先行論文を参考として顕性炎症(apparent inflammation) を持つ者とした[7]。中村らの研究結果を参考として，BNP値が50pg/mL以上をBNP高値と定義した[5]。尿中アルブミン指数が300mg/g 以上の場合を顕性アルブミン尿（Macroalbuminuria)，尿中アルブミン指数が30mg/g以上でかつ300mg/g未満を微量アルブミン尿と定義した[8),9)]。

追跡調査分析

平成18年9月の時点で，総参加者26,472名中二戸保健医療圏の参加者（該当者9,411名）について，登録後4年後の追跡調査（平均追跡期間3.8年）が終了した。追跡調査の内容は，住民異動情報による死亡・異動の把握，脳卒中発症登録事業による二戸地域の脳卒中患者の全数把握，心疾患発症登録事業による二戸地域の心筋梗塞患者数，心不全患者数，突然死数把握，二戸地域の介護情報収集による新規介護認定者の把握である。本稿では，二戸地域参加者の総死亡率，脳卒中罹患率を年齢階級別に明らかにした。また，特に脳卒中発症や新規介護認定を受けた者のリスク要因を解析する目的で，登録時の年齢が65歳以上でなおかつ，循環器疾患（脳卒中，心筋梗塞，心不全）の既往を有さない者，要介護あるいは要支援の認定を受けていない者を対象として解析を行った。観察人年は，介護認定日，脳卒中発症日，住民基本台帳確認日で違いがあることから，追跡調査解析にあたり，観察人年を各解析ごとに矛盾しないよう調整した。

統計解析手法

横断解析において，対象者間の連続変数の比較にはt検定を，度数や頻度の比較にはχ^2乗検定を用いた。3群以上の比較には一元配置分析を行い，多重比較にはBonferroni法を用いた。非正規分布をとる項目については，適宜ノンパラメトリック検定（Man-Whitney U検定やKruscal Wallis検定）を用いた。

追跡調査では生存分析の手法を用い，直接法による年齢調整には昭和60年の日本人基準人口を用い，マンテルヘンツェル法を用いて調整した。多変量調整による生存分析では，Coxの比例ハザードモデルを用いて，リスク要因の検定にはハザード比とその95％信頼区間を参考にした。p値は両側検定で算出し，0.05％未満を持って統計的有意性があると判断した。解析ソフトはSPSS version 11.0J を用いた。

結　果

表2には性別・年齢階級別の対象者の登録時属性―身体特性・血液検査項目・高血圧症有病率・糖尿病有病率・高脂血症有病率・心筋梗塞既往・脳卒中既往―を示す。この表で示された各疾患の有病率は，病院や診療所の患者記録ではなく，生活習慣問診で得られた情報を基にしている。80歳未満の男女では，BMI，収縮期血圧，HbA1cレベルは年齢が高いほど高くなっており，高血圧症有病率と糖尿病有病率も年齢が高いほど高かった。高脂血症有病率は，30歳以上の男性ではどの年齢階級でも30％前後で，女性では，50歳以上の女性で40％前後であった。肥満者の割合は，BMI25以上の軽度肥満者は，男女ともに35％前後，BMI30以上の高度肥満者は男5.5％，女3.0％であった。軽度肥満者の割合は年齢が高くなるほど高くなっ

ていた。一方高度肥満者の割合は，男性では80歳未満の全ての年代で５％前後であったのに対し，女性では年齢が高くなるほど高度肥満者割合は低かった。男女ともに高度肥満者割合が最も高かったのは20代であった。本研究参加者の心筋梗塞既往者，脳卒中既往者は各１％未満であり，日本人全体を対象とした推計値より低めである。これは，本研究参加者が健診受診者を対象としていることから，一般住民の中でも，比較的健康な者がより多く受診し，病気を持っている者が少なくなっている状況を反映している可能性がある。

表３は，参加者の生活習慣に関連する基本属性を性・年齢階級別に示したものである。50歳未満の男性の喫煙率は50％を超えており，本研究対象地域の喫煙率は非常に高い。女性の喫煙率は全体で３％未満と低いが，20代の喫煙率は20％を超えており，30代女性の喫煙率も15％と高めであり，若い女性の喫煙率が高いことが問題である。週５日以上飲酒する常用飲酒者は男性の30代から50代で50％を超えていた。月８回以上の運動習慣を持つ者（週２回程度の運動習慣を持つ者）の割合は男性で17.2％，女性10.6％で，30代から50代の働き盛りの男女では運動習慣を持つ割合は10％未満と低く，むしろ60代以降で高かった。

表４は，栄養調査によって得られた結果を，性別・年齢階級別に平均値を示したものである。たんぱく質・脂質・炭水化物の３大栄養素は，１日あたりの摂取量（g/day）を示すとともに，総カロリー摂取量に占める割合（% of total energy intake）の併記行っている。本研究参加者の総カロリー摂取量は男性でおよそ2500kcal，女性でおよそ1800kcalであり，女性の70歳未満の参加者では，年齢が高いほど摂取カロリーが高値であった。本研究参加者は食塩摂取量が非常に多いのが特徴である。男性では50歳以上の参加者の食塩摂取量平均値は15g/日を超えていた。女性では60歳以上で平均摂取量が13g/日を超えていた。また飽和脂肪酸摂取比率が低く，多価不飽和脂肪酸摂取比率が高いのも特徴である。飽和脂肪酸摂取比率は男性の平均が６％，女性で７％であり，多価不飽和脂肪酸摂取比率は男性の平均が６％，女性では７％であった。n-6/n-3摂取比率が低いこともこの研究参加者の特徴であり，男性で3.3，女性で3.4であった男女とも若い世代ほどn-6/n-3摂取比率は高かった。

表５は新しい予見因子として注目されている３項目の性・年齢階級別平均値を示している。高感度CRPの測定は，明らかな炎症性疾患を有していない対象者で，慢性の軽度の炎症（systemic low-grade inflammation）を評価することに使われ，動脈硬化症の活動性とならびにその予後との関連について最も多く使われているマーカである。尿中微量アルブミン測定は，顕性のアルブミン尿がみられていない健康人において，動脈硬化症の程度ならびにその予後との関連についてCRPと同様よく用いられるマーカである。一方BNPは，心不全の重症度とよく相関することが示され，一般健常人での測定についてはあまり普及していない。上記３マーカは，従来青壮年期の対象者で病気との関連や予後との関連いついて数多く検討されてきたが，健常人やことに高齢者での多数の検討例はあまり行われていない。本研究結果では，上記３マーカは年齢とともに上昇し，BNPに関しては，青壮年者の心不全を見極めるカットオフポイントである30pg/mLや50pg/mLは，70歳以上の対象者には不適切であることが示唆される。

表６は，性・年齢別の心房細動有病率を示している。心房細動有所見者は，男女ともに30代から認められ，男女ともに年齢とともに有病率は上昇し，男性の有病率がどの年齢階級でも高い。男性の心房細動有病率は50代で約１％，60代で３％，70代と80代５％であった。女性はそれぞれ0.2％，0.5％，1.4％，３％であった。循環器基礎調査で示された年齢階級別心房細動有病率に比べ，本研究参加者の心房細動有病率は高かった。

表７は，二戸地域の追跡調査結果得られた，総死亡・脳卒中の性年齢階級別発症数である。この地域での粗死亡率・脳卒中粗罹患率（/1000人年）はそれぞれ，男性で7.4，6.9であり，女性で3.1，3.8であった。二戸地域の人口構成で年齢調整す