Table 4
Crude means of CRP level and adjusted geometric means of CRP level by groups according to dietary intake of n-3PUFA, by groups according to dietary intake of EPA and DHA or by groups according to dietary intake of α linolenic acid

Dietary intake of n-3 PUFA (% of total energy)	Q1 Men (0.15–1.0%) Women (0.24–1.2%)	Q2 Men (1.0–1.4%) Women (1.2–1.5%)	Q3 Men (1.4–1.7%) Women (1.5–1.9%)	Q4 Men (1.7–4.2%) Women (1.9–6.4%)	Trend p
Male participants (n)	1088	1089	1089	1088	
CRP (mg/L)	0.91	0.85	0.84	0.85	
Adjusted CRP (mg/L)	0.54 (0.51–0.58)	0.48 (0.46–0.51)	0.48 (0.45–0.51)	0.46 (0.43–0.49)	<0.001
Female participants (n)	2461	2461	2461	2461	
CRP (mg/L)	0.74	0.71	0.65	0.75	
Adjusted CRP (mg/L)	0.44 (0.42–0.46)	0.43 (0.41–0.45)	0.41 (0.39–0.43)	0.42 (0.40–0.43)	0.011
Dietary intake of EPA & DHA (% of total energy)	Q1 Men (0.00–0.36%) Women (0.00–0.39%)	Q2 Men (0.36–0.57%) Women (0.39–0.63%)	Q3 Men (0.57–0.85%) Women (0.63–0.91%)	Q4 Men (0.85–3.4%) Women (0.91–4.3%)	Trend p
Male participants (n)	1088	1089	1089	1088	
CRP (mg/L)	0.89	0.86	0.84	0.85	
Adjusted CRP (mg/L)	0.52 (0.49–0.56)	0.50 (0.47–0.53)	0.48 (0.45–0.51)	0.46 (0.43–0.49)	0.002
Female participants (n)	2461	2461	2461	2461	
CRP (mg/L)	0.71	0.70	0.71	0.73	
Adjusted CRP (mg/L)	0.44 (0.42–0.45)	0.43 (0.41–0.44)	0.42 (0.40–0.44)	0.41 (0.40–0.43)	0.044
Dietary intake of α linolenic acid (% of total energy)	Q1 Men (0.13–0.55%) Women (0.18–0.68%)	Q2 Men (0.55–0.72%) Women (0.68–0.85%)	Q3 Men (0.72–0.92%) Women (0.85–1.1%)	Q4 Men (0.92–3.5%) Women (1.1–3.1%)	Trend p
Male participants (n)	1088	1089	1089	1088	
CRP (mg/L)	0.93	0.82	0.91	0.80	
Adjusted CRP (mg/L)	0.53 (0.50–0.56)	0.48 (0.46–0.51)	0.49 (0.46–0.52)	0.46 (0.43–0.49)	0.004
Female participants (n)	2461	2461	2461	2461	
CRP (mg/L)	0.76	0.70	0.69	0.70	
Adjusted CRP (mg/L)	0.44 (0.42–0.45)	0.42 (0.41–0.44)	0.42 (0.40–0.43)	0.42 (0.41–0.44)	0.207

Data are expressed as crude means or adjusted geometric means (95% CI). Adjusted geometric means of CRP level for persons aged 60 years with BMI of 24 (kg/m^2), SBP of 128 (mmHg), HDLC of 56.0 (mg/L), LDLC of 117.0 (mg/L) HbA1c of 5.10 (%), intake of saturated fatty acid of 5.5% of total energy, current smoking, ex-smoking, and regular drinking (mean). 95% CI (confidence interval) is based on standard errors from analysis of covariance.

quartile group were higher than those in each of the other three groups for the male subjects ($p < 0.05$, Mann–Whitney U test). On the other hand, there was no difference between mean crude CRP levels in the quartile groups for the female subjects. Higher intake of n-3PUFA was associated with lower percentage of smokers, lower percentage of drinkers, and higher percentage of subjects performing regular exercise.

Table 3 shows the results of multiple linear regression analyses using ln CRP as the dependent variable and smoking status patterns and other factors as independent variables. "Current smoking" and "ex-smoking" were significantly correlated with ln CRP levels in the male subjects but not in the female subjects. Age, BMI, systolic blood pressure, levels of HDLC, LDLC, and HbA1c, intake of SFA, and intake of n-3PUFA were related to ln CRP level in both sexes. Regular drinking was also correlated with ln CRP level, but regular exercise was not associated with ln CRP level. The high levels of correlation among the explanatory variables produce challenges for statistical modelling to ensure the results are not artifacts of collinearity. We also performed multiple regression analyses using the products of pairs of explanatory variables as independent variables to adjust for interactions between explanatory variables. The results were unchanged even after adjusting for interactions between explanatory variables (data not shown).

Non-adjusted and adjusted geometric mean levels of CRP in the quartile groups according to intake of n-3PUFA, according to intake of long-chain n-3PUFA, or according to intake of ALA are shown in Table 4. Multiple comparisons showed significant difference only between the Q1 category and Q4 category according to intake of n-3PUFA (0.54 vs. 0.46, $p < 0.05$) in male subjects. Linear trends across quartile groups according to intake of n-3PUFA or according to intake of long-chain n-3PUFA existed both in male and female subjects. The higher the intake of n-3PUFA was, the lower adjusted CRP level was. The higher the intake of long-chain PUFA was, the lower the adjusted CRP level was. A linear trend across quartile groups according to intake of ALA existed only in male subjects. In female subjects, slightly elevated CRP levels in Q1 and equal levels in Q2, Q3, and Q4 categories were observed.

Table 5 shows adjusted geometric means of CRP level in the quartile groups separately by smoking status. Linear trends across quartile groups were shown in both smokers and ex-smokers in the male subjects. Multiple comparisons showed significant differences in CRP levels between the Q1 and Q2 categories, between the Q1 and Q3 categories, and between the Q1 and Q4 categories in male smokers (0.54 vs. 0.48, 0.48, 0.48, or 0.46, $p < 0.05$). The difference between CRP levels in the Q1 and Q4 categories was also significant in male ex-smokers. A significant difference was not

Table 5
Adjusted geometric means of CRP level in the quartile groups according to dietary intake of n-3PUFA separately by smoking status

Dietary intake of n-3 PUFA (% of total energy)		Q1 Men (0.15-1.0%) Women (0.24-1.2%)	Q2 Men (1.0-1.4%) Women (1.2-1.5%)	Q3 Men (1.4-1.7%) Women (1.5-1.9%)	Q4 Men (1.7-4.2%) Women (1.9-6.4%)	trend p
Male nonsmokers	(n)	336	374	411	426	
Adjusted CRP	(mg/L)	0.43 (0.38-0.48)	0.42 (0.38-0.46)	0.42 (0.38-0.46)	0.39 (0.35-0.43)	0.232
Male ex-smokers	(n)	323	306	320	312	
Adjusted CRP	(mg/L)	0.57 (0.51-0.64)	0.48 (0.43-0.54)	0.47 (0.42-0.52)	0.46 (0.41-0.51)	0.009
		Q1 vs. Q4: $p < 0.05$				
Male smokers	(n)	429	407	357	350	
Adjusted CRP	(mg/L)	0.54 (0.51-0.58)	0.48 (0.46-0.51)	0.48 (0.45-0.51)	0.46 (0.43-0.49)	0.029
		Q1 vs. Q2: $p < 0.05$; Q1 vs. Q3: $p < 0.05$; Q1 vs. Q4: $p < 0.05$				
Female nonsmokers	(n)	2,310	2,343	2,358	2,388	
Adjusted CRP	(mg/L)	0.44 (0.42-0.46)	0.43 (0.41-0.44)	0.41 (0.39-0.42)	0.41 (0.39-0.43)	0.005
Female ex-smokers	(n)	48	43	36	21	
Adjusted CRP	(mg/L)	0.43 (0.31-0.60)	0.47 (0.32-0.67)	0.52 (0.36-0.77)	0.68 (0.42-1.09)	0.097
Female smokers	(n)	101	74	66	52	
Adjusted CRP	(mg/L)	0.56 (0.44-0.71)	0.48 (0.37-0.63)	0.41 (0.31-0.55)	0.58 (0.43-0.79)	0.605

Data are expressed as adjusted geometric means (95% CI). Adjusted geometric means of CRP level for persons aged 60 years with BMI of 24 (kg/m^2), SBP of 128 (mmHg), HDLC of 56.0 (mg/L), LDLC of 117.0 (mg/L) HbA1c of 5.10 (%), intake of saturated fatty acid of 5.5% of total energy, and regular drinking (mean). 95% CI (confidence interval) is based on standard errors from analysis of covariance. p values were determined by analysis of covariance. Multiple comparisons were performed using Bonferroni's method.

found in CRP levels between the groups in male nonsmokers. Although differences in CRP levels between groups were small, a significant linear trend across the quartiles was found in female nonsmokers.

3. Discussion

The main findings of this study were (1) adjusted CRP levels were inversely associated with dietary intake of n-3PUFA or dietary intake of long-chain n-3PUFA for both the male subjects and female subjects, (2) the inverse relationship between adjusted CRP levels and dietary intake of n-3PUFA was more evident in smokers than in nonsmokers in the male subjects, and (3) male smokers taking a low dose of n-3PUFA (in the lowest quartile group) had significantly higher levels of adjusted CRP than those in other male subjects.

Although a linear trend between dietary intake of n-3PUFA and serum CRP levels exists, we also plotted the adjusted geometric mean CRP levels in 20 equally partitioned subgroups according to their intake of n-3PUFA in order to show a non-linear effect between CRP levels and intake of n-3PUFA. An interpolation curve obtained by using spline function showed a steep descent between categories 2 and 3 and a gradual descent between C3 and C20. The spline curve suggests that a cutoff point exists at the C3 point (i.e., 0.91% of energy) and this point possibly means n-3PUFA requirement to maintain attenuated inflammatory reaction (see additional figure as supplementary appendix).

This study also revealed gender-based differences in CRP levels. However, when subjects were limited to nonsmokers, the adjusted CRP levels were almost the same in the male and female subjects (0.42 mg/L in male nonsmokers vs. 0.44 mg/L in female nonsmokers). Considering the low rate of smoking among women and the high rate of smoking among men in this study, the sex-based difference in adjusted CRP levels is probably due to the difference in smoking prevalence between men and women.

The results of this study suggest that activated inflammation is independently attenuated by high-dose dietary intake of n-3PUFA, especially in male smokers. Since n-3PUFAs are precursors of anti-inflammatory eicosanoids (such as prostaglandin I3, prostaglandin E3, thromboxane A3, and leukotriene B5), n-3PUFAs are hypothesized to attenuate the inflammatory response [23,24]. Several studies have been carried out to determine the associations between dietary intake of n-3PUFA (or fish) and levels of inflammatory markers. Pischon et al. showed that dietary intake of n-3PUFA was inversely associated with plasma levels of soluble tumor necrosis factor (TNF) receptors and somewhat less with C-reactive protein in healthy men and women [23,25]. Ciubotaru et al. showed that dietary fish oil reduces levels of C-reactive protein and interleukin-6 in postmenopausal women undergoing hormone replacement therapy (HRT) [26]. These studies suggest that intake of n-3PUFA (or fish) decreases the levels of inflammatory cytokines and CRP levels in healthy subjects. The effect of n-3PUFA intake on serum CRP levels is more evident in high-risk subjects, such as women undergoing HRT. Some studies showed that both CRP levels and other inflammation-related markers were influenced by intake of n-3PUFA. However, we did not measure the levels of interleukins, TNF-alfa, or other inflammation-related agents such as matrix metalloproteinase or macrophage colony-stimulating factor, and we therefore can not discuss the possibility of effects on different inflammation-related pathways due to n-3PUFA.

Rodriguez et al. showed that the favorable effects of fish consumption were more evident in male smokers than that in male nonsmokers in Japanese Americans living in Hawaii [17]. Notably, the apparent preventive effects of fish consumption on cardiac events in their study and the apparent anti-inflammatory effect of dietary intake of n-3PUFA in our study are commonly observed in male smokers. Although the underlying biochemical mechanism was not discussed in their report, the anti-inflammatory effects of n-3PUFA are thought to contribute to the mechanisms that decrease cardiac events in heavy-smoking males.

Several limitations to our study should be noted. The cross-sectional design of the present study tolerates uncertainty of causal relationships. A single instance of blood sampling may be susceptible to short-term variation. Because determination of dietary variables, including fatty acid, was based on a self-administered food frequency questionnaire, information on dietary variables might have been overestimated or underestimated. Socio-economical status (SES) is one of the important confounding factors. However, there was little information about SES in this study and this is one of the limitations. Exercise habit is also one of the important factors that are associated with CRP levels. We performed regression analysis using exercise-related variables and other factors as explanatory variables in three ways: regular exercise, times per month, and quartile categories. There was no relationship between exercise habit and CRP levels in any of the three patterns. We thought that information about exercise in this study was not sufficient for adjusting for confounding effects. The small numbers of female ex-smokers (1.5%) and female nonsmokers (3%) limited statistical power to draw strong conclusions about these groups. The small number of individuals who consumed small amount of n-3PUFA was also one of the limitations.

Despite the lack of causal relationships, based on our findings and those of others, it is reasonable to conclude that sufficient dietary intake of n-3PUFA may attenuate inflammatory reaction and that this effect is more evident in high-risk populations such as male smokers.

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

Appendix A

A.1. Members of Iwate-KENCO Study

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

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

Appendix B. Supplementary data

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

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Cardiovascular risk factors in the Japanese northeastern rural population ☆

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Abstract

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

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

1. Introduction

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

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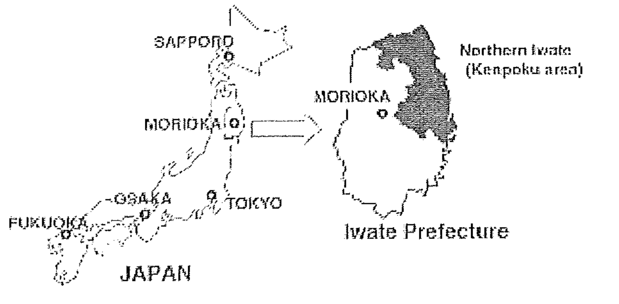

Fig. 1. The study area. This figure shows a map of Japan and a map of Iwate Prefecture. Iwate Prefecture is located in the northeastern part of the main island (Honshu Island) of Japan. The black area of Iwate Prefecture indicates the study area. Kenpoku means northern part of the prefecture in Japanese.

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

2. Subjects and methods

2.1. Study subjects

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

2.2. Measurements

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

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

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

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

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

Data are expressed as numbers or percentages.

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

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

2.3. Biochemical analyses

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

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

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

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

2.4. Classification and definition

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

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

2.5. Statistical analysis

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

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

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

3. Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

[a] Excluding high hsCRP level (≥10 mg/L).
[b] Proportion of high BNP level (≥50 pg/mL).
[c] Excluding macroalbuminuria (UACR ≥300 mg/g).
[d] Proportion of microalbuminuria (≥30 mg/g).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix A. Members of the Iwate-KENCO Study

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原　著

C型肝炎と透析患者-岩手県透析患者コホート研究から判明した透析患者のC型肝炎感染の実態

大　澤　正　樹

要　　約

透析患者は腎不全のみならず種々の合併疾患を有していることが多く，合併疾患に係る病状の悪化も患者の生活の質を下げ，また合併症の存在自体が透析患者の医療費を増大させている要因の一つと考えられる。透析患者の合併疾患の一つであるC型肝炎は，その有病率の高さのみならず透析患者の予後を悪化させていることから注目されている。本稿では，岩手県で実施している透析患者コホート研究（カレン研究）で得られた知見を基に一般住民と比較して透析患者のC型肝炎標準化有病比を明らかにするとともに，C型肝炎感染が透析患者の死亡リスクを上げているのか，上げているとしたらどのような死因によって死亡リスクが上がっているのかについて検討した。

カレン研究により以下のことが明らかとなった。1）透析患者の11%がC型肝炎抗体陽性であり，感染既往者は4.5%，持続感染者は6.5%であった。2）透析患者のC型肝炎の標準化有病比は，抗体陽性者で判定すると男性で8.39，女性で5.42，抗原陽性（持続感染）者の標準化有病比は男性で12.9，女性で8.77であった。3）女性透析患者ではC型肝炎持続感染者の割合が男性より低かった。4）C型肝炎持続感染者は非感染者と比較して，血清脂質値が低く，血清アルブミン値が低かった。5）透析患者の死亡率は93.4（/1000人年），C型肝炎非感染群の死亡率は88.7，感染既往群の死亡率は123.2，持続感染群の死亡率は142.8であった。6）C型肝炎持続感染による死亡リスクの上昇は，女性透析患者でより顕著であった。7）C型肝炎持続感染群の死亡率の高値には，循環器疾患死亡率ならびに肝不全死亡率の高さが寄与していた。8）C型肝炎持続感染群で循環器疾患死亡率を押し上げていた要因は，脳出血死亡と心不全死亡であった。9）C型肝炎持続感染群の脳出血死亡者の特徴は，血圧高値ではなく，やせ，血清脂質とアルブミンの低値，CRPの高値であった。10）種々のリスク要因で調整した多変量解析の結果，C型肝炎持続感染は透析患者の死亡リスクを2.3倍高めていた。男性では1.8倍，女性では3.2倍死亡リスクが高かった。11）多変量解析の結果C型肝炎感染既往は，透析患者の死亡リスクを1.7倍高めていた。12）C型肝炎持続感染は，男性透析患者の循環器疾患死亡リスクを1.8倍，女性透析患者の循環器疾患死亡リスクを4.2倍上げていた。13）C型肝炎持続感染は，女性透析患者の感染症死亡リスクを3.6倍高めていたが，男性患者では明らかな影響は観察されなかった。

上記知見は，日本人透析患者の地域ベースの研究で明らかにされた日本で最初の疫学研究成果であり，全て資料的価値の高い知見と言える。日本人透析患者のC型肝炎対策を企画するにあたり，貴重な資料として活用されることが期待される。

（本稿は，平成18年度厚生労働科学研究費補助金（肝炎等克服緊急対策研究事業）平成20年度分担研究者報告書を，ご協力いただいた岩手県内関係者に遍く公表開示することを目的に一部を改変編集して当雑誌に寄稿したものである）

Keywords：透析患者，型肝炎，有病率，死亡率，疫学研究

岩手医科大学医学部衛生学公衆衛生学講座

1．はじめに

透析患者は日本全体で26万人を超え，その数は年々増加している。近年は予後が不良とされる糖尿病性腎症による透析導入患者が急増しており，日本人透析患者の死亡率は9％前後で推移し，その半数は循環器疾患で死亡しているものと推測されている[1]。

一方，透析患者は腎不全のみならず種々の合併疾患を有していることが多く，合併疾患に係る病状の悪化も患者の生活の質を下げ，また合併症の存在自体が透析患者の医療費を増大させている要因の一つと考えられる。透析患者の合併疾患としては，高血圧症を初めとして循環器疾患が代表的であるが，近年はＣ型肝炎にも注目が集まっている。その理由として，そもそも日本人全体の1％が抗Ｃ型肝炎抗体を有し[2]，肝臓がんの原因の90％をＣ型肝炎が占めることから一般住民にとっても大きな健康問題となっていること，その中で透析患者のＣ型肝炎抗体陽性率は一般住民の10倍近いことが示唆され，Ｃ型肝炎感染が透析患者の予後を悪化させていることが示唆されているからである[3]。

透析患者の生活の質（QOL）を高め予後を改善するためには，透析治療そのものの技術革新が必須であるが，合併症に係る問題点を解決することも必要である。本稿では，岩手県北部地域で実施している透析患者コホート研究で得られた知見をもとに現在の日本人透析患者のＣ型肝炎感染状況を提示し，その問題点と解決すべき問題点を提示したい。

2．岩手県透析患者のＣ型肝炎感染の状況

平成18年度から始まった厚生労働省科学研究費補助金事業（肝炎等克服緊急対策研究事業：透析施設におけるＣ型肝炎院内感染の状況・予後・予防に関する研究）H18-肝炎-2，主任研究者　秋葉隆）は，Ｃ型肝炎感染のハイリスクであり，なおかつ有病率が非常に高い透析患者の現状を疫学研究によって把握するとともに，院内感染の予防ガイドライン作成と治療法の確立を目指して始められた多施設共同研究である[4]。

この研究事業の分担研究者藤岡は，岩手県で平成15年度から透析患者の地域悉皆的コホート研究（カレン研究）を主導し，94万人の人口を要する地域で，1506名の成人血液透析患者の81％を登録した実績を持つ。カレン研究はリスク要因として循環器疾患危険因子と心筋梗塞・脳卒中既往などを取り上げ，エンドポイントとしての循環器疾患発症ならびに循環器疾患死亡を登録することで進められてきた。今回の厚生労働科学研究助成―肝炎等克服研究事業―を受けて，新たにリスク要因としてＣ型肝炎の有病状況を加え，エンドポイントにはがん死亡，肝疾患関連死亡ならびに感染症死亡なども取り込んで，Ｃ型肝炎感染が透析患者の死亡リスクにどのような死因に影響を与えて死亡リスクを挙げるのか，また透析患者ではＣ型肝炎感染により，肝不全や肝細胞がん死亡が（統計学的有意差検定に耐えうるデータを供する意味で）増加するのかどうか，といったまだ明らかにされていない課題についても明らかにすべく，調査対象内容を大幅に増やしてコホート研究内容の充実を図った[4]。

本稿では，研究のプラットフォームとして透析患者のＣ型肝炎の疫学研究の土台となったカレン研究について概要を述べ，透析患者とＣ型肝炎感染に焦点を当てた三つの研究課題：1）透析患者と一般住民とのＣ型肝炎有病率比較，2）透析患者におけるＣ型肝炎感染患者と非感染者との属性の違い，3）Ｃ型肝炎感染の透析患者の予後に及ぼす影響，についてそれぞれ方法，結果，解釈ならびに考察を分けて記述し，最後に本研究で得られた透析患者のＣ型肝炎感染に関する，特に疫学的な面で資料的価値が高いと考えられる新知見と，新たに生じた研究課題について述べてみたい。

カレン研究概要

藤岡らは平成15年から岩手県北部で成人血液透析患者の地域悉皆コホート研究を実施している。カレン研究（末期腎不全患者に対する多面的な取り組みにより循環器疾患発症リスクを割り出す研

究：Kaleidoscopic Approaches to patients with end-stage RENnal disease, KAREN研究）と名づけられた本研究の対象地域は岩手県北部から県中央部で，平成14年当時の域内には38市町村が含まれ，総人口は939,448人である。カレン研究では，20歳以上の成人透析患者を研究対象とした。透析施設は全部で26施設あり，成人透析患者総数は1,506名であった。人口100万人あたりでは透析患者は1,596人であった（図1）。登録調査は2003年6月に始まり，2004年3月まで行った。本研究は岩手医科大学倫理審査委員会の承認を得て，ヘルシンキガイドラインに従って実施された[5), 6)]。

カレン研究参加者

研究参加者の内訳を図2に示す。25施設1,499名の透析患者の内，全身状態不良者または脳血管性認知症などにより意思疎通が困難だった27名は面会できなかった。残りの1,447名に面会し，1,260名から書面による同意（登録時調査ならびに1年毎の追跡調査に対する）を得た（同意受容率87.0%）。同意が得られた1,260名中21名は病状の悪化や転院により登録調査ができなかった。25名の患者では血液検査がなされなかった。1年ごとに25透析施設を直接訪問して，1,214名の透析患者診療記録を閲覧した。本報告書では，透析患者のC型肝炎標準化有病比算出ならびに透析患者の横断解析研究では1,214名の透析患者データを用いた。縦断研究においては，平成21年1月の時点で転院先での追跡調査が終了していないものが6名存在していることから，4年分の追跡調査が終了した1,208名を縦断研究解析対象として検討した。

カレン研究登録調査

登録調査は，2003年6月から2004年3月まで岩手県内25透析施設を直接研究者や研究補助が訪問して行った。調査内容は，調査員の面談による生活問診，血圧測定，身長測定，患者医療記録による患者医療情報収集，透析施行直前の採血による血液検査である。登録時調査の詳細については，すでに公表している論文を参照されたい[5), 6)]。

C型肝炎感染状況調査

平成18年度の厚生労働省科学研究費補助金事業（肝炎等克服緊急対策研究事業：透析施設におけるC型肝炎院内感染の状況・予後・予防に関する研究，主任研究者：東京女子医科大学腎臓病総合

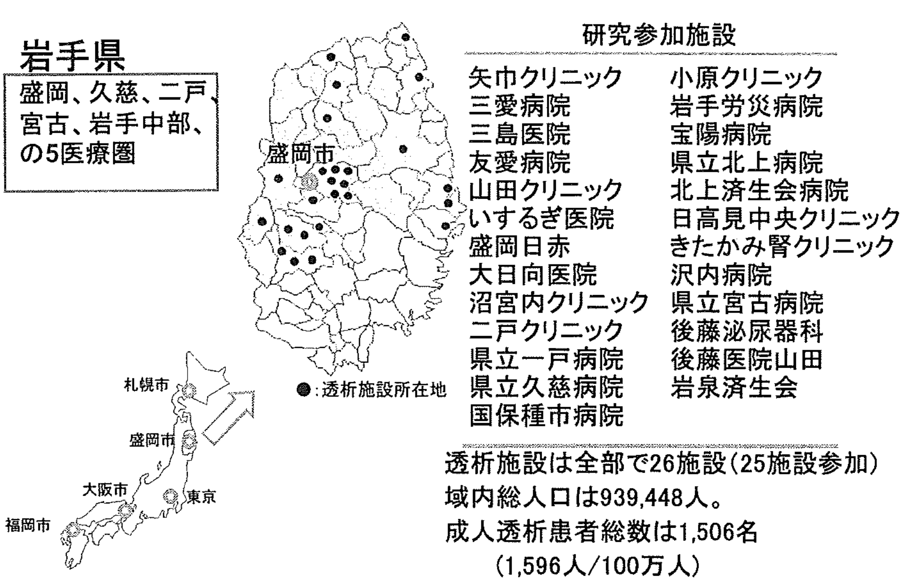

図1　カレン研究対象地域

図は日本地図と岩手県地図を示す。岩手県地図において，灰色で塗りつぶされた部分がカレン研究の行われた保健医療圏（二戸地区，久慈地区，宮古地区，盛岡地区，岩手中部地区（遠野市を除く）を示す。●印は透析施設の存在する市町村を示す。域内26施設中25施設が研究に参加した（平成15年当時）。

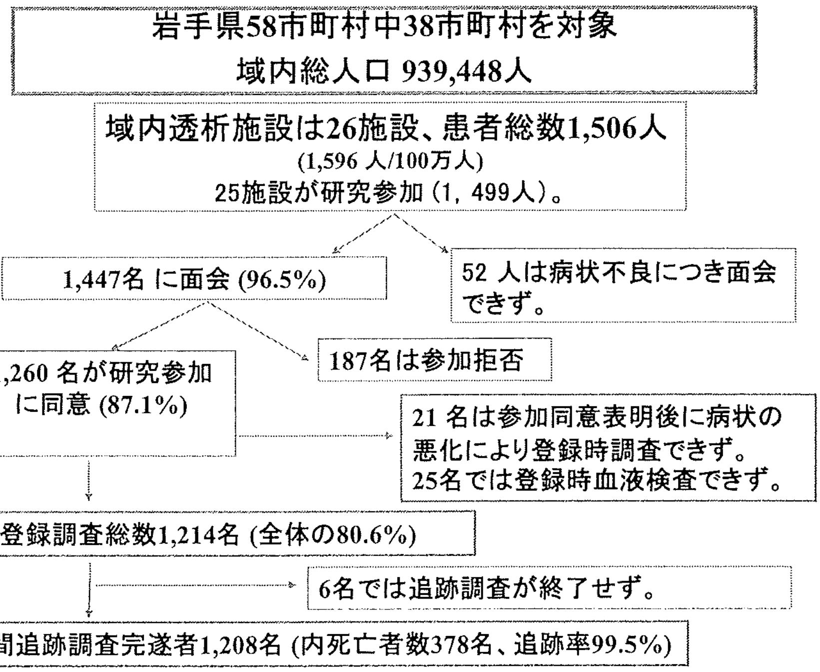

図2 カレン研究参加者フローチャート

図はカレン研究に参加した透析患者の登録フローチャートである。1506名の成人血液透析患者の存在を確認し，面会のできた1447人のインフォームドコンセントを実施した。最終的に1214名の患者で登録時調査を完遂した。

医療センター 秋葉 隆；分担研究者：岩手医科大学泌尿器科学講座 藤岡知昭；研究協力者：岩手医科大学衛生学公衆衛生学講座 大澤正樹）の研究費補助金を受けて，上記カレン研究に新たにC型肝炎の有病状況について調査が加えられた[4),7)]。従来から継続して行われていたカレン研究に追加して平成18年度に付け加えられた調査内容は以下の二つである。

透析患者のC型肝炎調査

C型肝炎有病状況調査は，吉澤らが実施している，厚生労働省科学研究費補助金肝炎克服研究事業（H16-肝炎-3）で定められたスクリーニングの手順に則って行った[8)]。平成15年度に登録された1,214名の透析患者のC型肝炎有病状況調査は，まずすべての患者カルテの閲覧を行って各透析施設で行っているC型肝炎抗体検査の結果を書き写す作業から始められた。研究に参加した25透析施設の検査担当者に直接または電話での問い合わせを行い，C型肝炎抗体検査が第2世代または第3世代のELISA測定キットを用いて行われていることを確認した。1,214名中50名ではカルテ閲覧によってはC型肝炎抗体検査結果を知ることはできなかった。これらの50名では，平成15年当時に採取された血清の凍結検体を解凍して，三菱メディエンス盛岡支社に依頼して，C型肝炎抗体検査（アボットジャパン，Architect C型肝炎 測定キット）を行った。C型肝炎抗体陽性者は引き続きC型肝炎コア抗原検査を行い，抗原定量を実施した。C型肝炎コア抗原定量はCLEIA法を用いて測定した。尚，C型肝炎抗体陽性でなおかつ抗原定量検査で陰性と判断された55名ではPCR法によるC型肝炎RNAの定量は，検体量が少なかったため実施できなかった（図3参照）[7)]。

一般住民のC型肝炎スクリーニング

透析患者のC型肝炎有病率を算出するとともに，透析患者が一般人と比較して何倍の割合でC型肝炎に感染しているのかを知る目的で，透析患者と同じ地域に住む一般住民の有病率を基準として標準化有病比（standardized morbidity ratio）を求めた。C型肝炎の有病率には地域差があることが

HCV 持続感染ならびに感染既往の同定手順

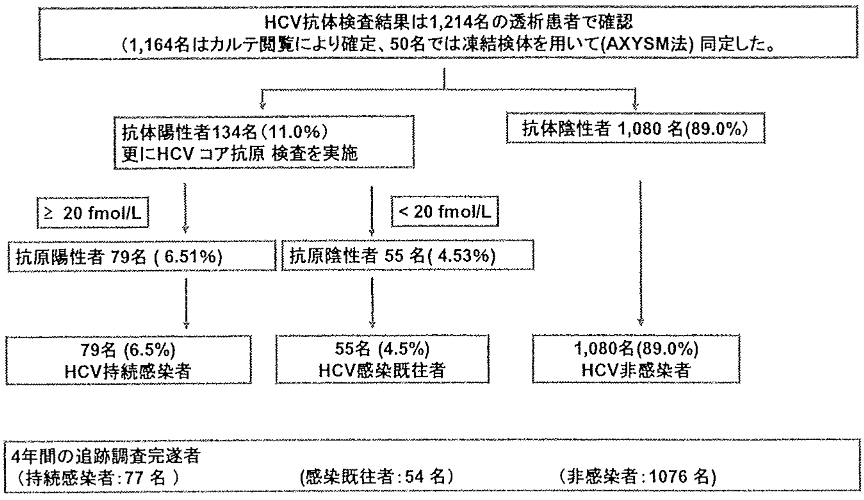

図3　透析患者のC型肝炎持続感染/感染既往/非感染の同定手順

図は透析患者のHCV感染状況同定手順を示す。1214名の患者のカルテ閲覧により1164名で抗HCV抗体検査の結果を確認した。残り50名では，登録調査時に実施した採血検査の残存凍結血清を解凍して抗HCV抗体検査を実施した。抗HCV抗体陽性であった134名では，凍結血清を解凍してHCVコア抗原定量検査を実施した。79名でコア抗原検査が陽性であった。HCVコア抗原検査が陰性であった者は55名で，追加のHCVRNA定量検査は施行しなかった。

知られていることから[2]，透析患者の在住する岩手県の一般住民を比較対照とした。本研究では，吉澤らの厚生労働省科学研究費補助金肝炎克服研究事業（H16-肝炎-3）の分担研究者として岩手県でのC型肝炎スクリーニング調査を実施している阿部弘一班員の岩手県C型肝炎スクリーニングのデータを用いた[8]。岩手県C型肝炎スクリーニングのデータ使用にあたり，吉澤研究班員の阿部弘一研究員にも本研究（秋葉班研究）の研究協力者に入ってもらうとともに，データを管理する岩手県予防医学協会と本研究代表者藤岡知昭がデータ使用に関しての覚書の取り交わしを行ったうえで岩手県C型肝炎スクリーニングのデータを厚生労働科学研究費補助金事業の一環としての透析患者のC型肝炎有病状況研究の成果公表に用いることを確認のうえ研究は進められた。

ここで岩手県C型肝炎スクリーニングについて概要を触れる。

岩手県では岩手県予防医学協会が実施している健診事業に際して，C型肝炎の有病状況調査を2003年から実施している。本研究の対照として用いたのは，2005年のスクリーニング調査データである（図4参照）。22,474名の健診受診者でC型肝炎抗体検査が行われた。C型肝炎抗体が高力価であった73名は持続感染者と判断。抗体価が中等度であった281名では引き続きC型肝炎コア抗原検査が行われた。抗体検査が陰性であった22,120名は，C型肝炎非感染例と判断した。抗体陽性者281名中45名ではC型肝炎コア抗原定量検査でも陽性と判断された。コア抗原検査が陰性であった236名ではPCR法によるC型肝炎-RNA定量が行われた。その結果，コア抗原検査陰性者でC型肝炎-RNA定量検査で陽性であった者は1名も存在していなかった。透析患者と一般人の比較研究では，C型肝炎抗体陽性の有病率とC型肝炎コア抗原陽者の有病率の両者を算出して，透析患者におけるC型肝炎感染標準化有病比を算出した。

カレン研究追跡調査

カレン研究追跡調査は研究者（大澤正樹，加藤香廉，板井一好，丹野高三，藤島洋介）と訓練された研究看護師（古沢智子，白藤朋子，沢田美代

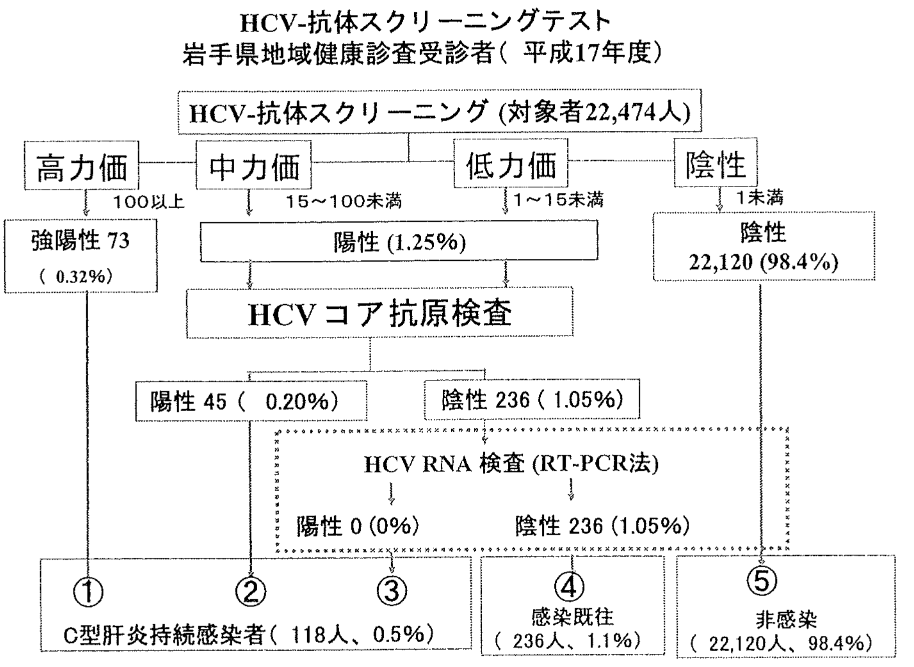

図４　岩手県一般住民におけるＣ型肝炎感染スクリーニング手順

図は岩手県内市町村の健康診査を受診した一般住民を対象として実施したＣ型肝炎スクリーニングの手順を示したものである。このスクリーニング手法は，吉澤らの提案したＣ型肝炎感染診断のガイドラインに沿ったものである。岩手県一般住民においては抗HCV抗体陽性者は1.6％と存在し，持続感染者と判断された者は全体の0.5％であった。HCVコア抗原が陰性でHCVRNAテストが陽性であった者は一人もいなかった。

子，佐藤佳乃子，畠山雅子）が直接透析施設を毎年訪問して，患者診療記録ならびに死亡診断書を閲覧して死亡と死亡原因，循環器疾患発症（冠動脈疾患，心不全，脳血管疾患）の有無，悪性新生物発症の有無について登録している[4]。死亡原因同定と疾患発症同定に関しては，カレン研究開始時に研究チームで協議して一定の基準を設けた[6]。疾患定義は表１に示したとおりである。尚，脳卒中の診断基準において，脳出血，脳梗塞，くも膜下出血の診断は，画像診断で確認したものとした。転院した症例に関しては，転院先を訪問し，患者診療記録を閲覧して情報収集した。心筋梗塞や脳卒中発症に関しては，カルテ閲覧により症状発現が明らかな場合は症状発現日時を発症日時とし，症状発現日時が明らかでない場合には，医師による診断が下された日時を発症日とした。悪性新生物の発症日は，画像診断による診断や生検による病理組織検査での確定がなされた日時を発症日とした。

統計ならびに解析手法

１）Ｃ型肝炎感染標準化有病比

一般住民ならびに透析患者を男女別に10歳階級ごとに（20-29，30-39，40-49，50-59，60-69，70歳以上）７グループに分け，年齢階級別にＣ型肝炎抗体陽性率，Ｃ型肝炎コア抗原陽性率を算出した。次いで一般住民を基準人口として，透析患者のＣ型肝炎抗体陽性標準化有病比ならびにＣ型肝炎コア抗原陽性標準化有病比を求めた。

透析患者を男女別に透析治療期間５グループ（半年未満，半年から１年未満，２年から５年未満，５年から10年未満，10年以上）にわけ，グループ別にＣ型肝炎抗体陽性率ならびにＣ型肝炎コア抗原陽性率を求めた。男女での有病率比較と透析治療期間の２群比較には，χ二乗検定により有意差検定を行った。

２）カレン研究横断解析

1,214名の研究参加者の属性をみるにあたり，まず性別で属性比較を行い，予後に影響すると考