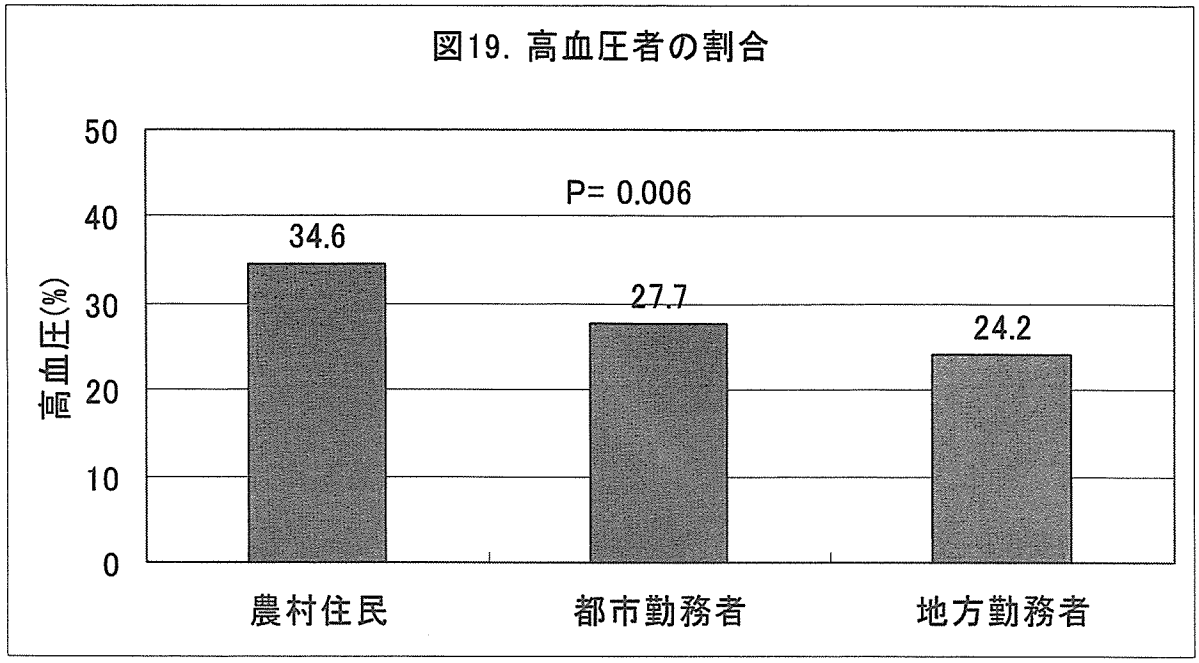
図19. 高血圧者の割合
高血圧(%)
50
40
30
20
10
0
P= 0.006
34.6
27.7
24.2
農村住民
都市勤務者
地方勤務者

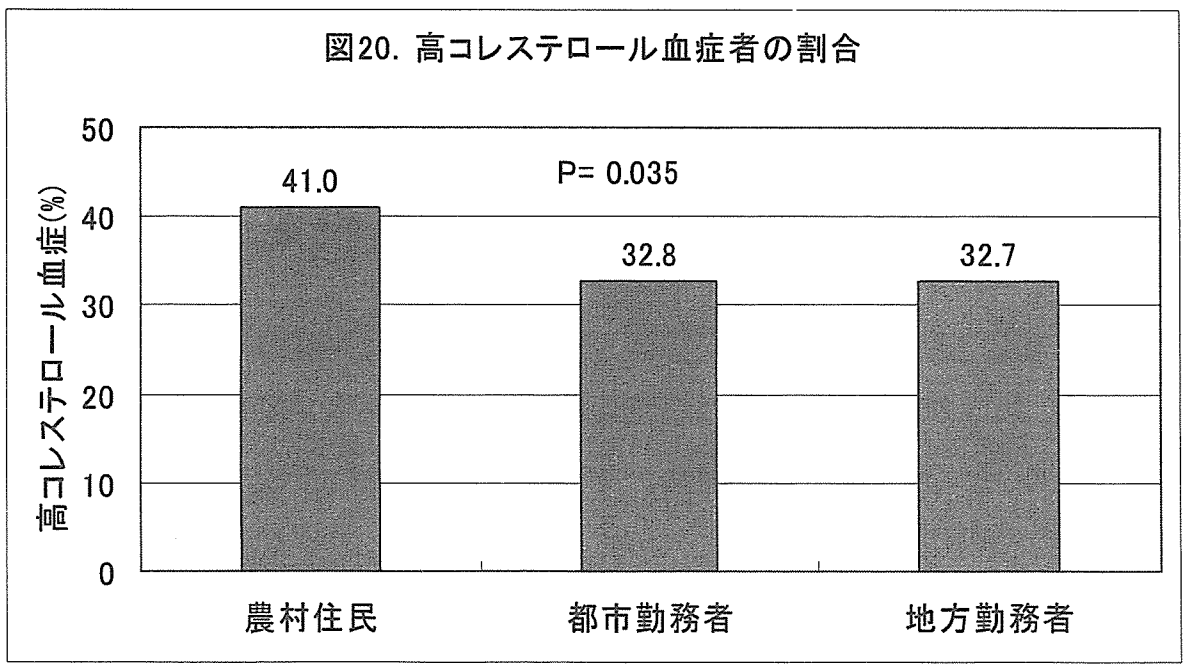
図20. 高コレステロール血症者の割合
高コレステロール血症(%)
50
40
30
20
10
0
P= 0.035
41.0
32.8
32.7
農村住民
都市勤務者
地方勤務者

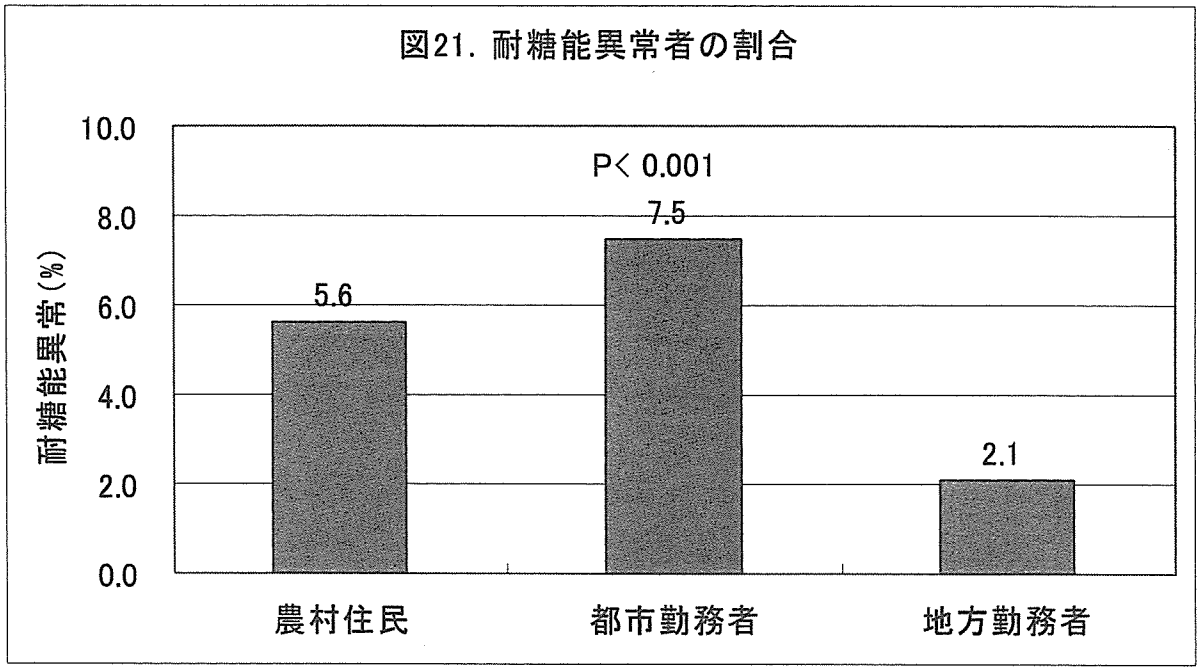

表1. 地方勤務者と比べた都市部勤務者と農村住民の収縮期血圧値の差(重回帰分析による偏回帰係数の算出)

分析モデル	集団	偏回帰係数	標準誤差	標準化係数	有意確率	決定係数(自由度調整済み)
Model 1	農村住民	4.17	0.815	0.085	P <0.001	0.087
	都市部勤務者	−1.42	0.547	−0.043	P <0.001	
Model 2	農村住民	4.86	0.771	0.101	P <0.001	0.206
	都市部勤務者	−1.29	0.524	−0.039	0.014	
Model 3	農村住民	3.55	0.861	0.081	P <0.001	0.214
	都市部勤務者	−1.58	0.604	−0.047	0.009	

注)Model 1: 年齢調整、Model 2: 年齢、BMI、飲酒量調整、Model 3: 年齢、BMI、飲酒量、塩分排泄量調整

表2. 地方勤務者と比べた都市部勤務者と農村住民の拡張期血圧値の差(重回帰分析による偏回帰係数の算出)

分析モデル	集団	偏回帰係数	標準誤差	標準化係数	有意確率	決定係数 (自由度調整済み)
Model 1	農村住民	1.54	0.560	0.042	P <0.001	0.227
	都市部勤務者	−1.42	0.376	−0.057	0.006	
Model 2	農村住民	2.09	0.529	0.058	P <0.001	0.333
	都市部勤務者	−1.27	0.359	−0.051	P <0.001	
Model 3	農村住民	2.07	0.594	0.063	0.001	0.319
	都市部勤務者	−0.98	0.417	−0.039	0.019	

注)Model 1: 年齢調整、Model 2: 年齢、BMI、飲酒量調整、Model 3: 年齢、BMI、飲酒量、塩分排泄量調整

表3. 地方勤務者と比べた都市部勤務者と農村住民の高血圧有病率オッズ比

分析モデル	集団	オッズ比	95%信頼区間	有意確率
Model 1	地方勤務者	1.00		
	農村住民	1.42	1.03, 1.96	0.031
	都市部勤務者	1.19	0.94, 1.52	0.155
Model 2	地方勤務者	1.00		
	農村住民	1.57	1.12, 2.21	0.090
	都市部勤務者	1.31	1.01, 1.70	0.040
Model 3	地方勤務者	1.00		
	農村住民	1.63	1.12, 2.39	0.013
	都市部勤務者	1.31	0.97, 1.76	0.083

注)Model 1: 年齢調整、Model 2: 年齢、BMI、飲酒量調整、Model 3: 年齢、BMI、飲酒量、塩分排泄量調整

三　部

考　察

考察

本研究では、滋賀県T郡住民の循環器疾患危険因子の状況を把握し、都市部（東京、大阪近郊）の勤務者、北陸にある地方事業所の勤務者と比較した。農村部住民と勤務者の年齢構成が大きく異なるため、直接比較可能な年齢層、すなわち40～54歳の範囲に絞り、平均値で示される指標についてはさらに年齢調整を行いそのレベルを比較した。その結果、農村部住民で血圧値、塩分排泄量が高く、HDLコレステロール値が低い傾向を認めた。またBMIも農村住民で最も大きくなっていた。一方、血糖値と飲酒率は勤務者で高かった。なお都市部と地方の勤務者同士を比較すると、塩分排泄量は地方のほうがやや高いものの両群の血圧レベルには差がなかった。またHDLコレステロールレベルは地方のほうが良好だったが、血清総コレステロールと喫煙率は都市に比し高かった。その結果、予測される将来の虚血性心疾患発症リスクは、地方勤務者を1.00とした場合、都市勤務者で0.94、農村部住民で1.54となり、農村部住民のリスクは約50%高いことが明らかとなった。農村部住民において勤務者よりも良好な値を示した血糖値が推計に用いたCox回帰係数に含まれていないという面はあるものの、このリスク差は非常に大きいと考えられる。

高血圧は循環器疾患の危険因子の中でもっとも頻度が高い要因であるが(1)、滋賀県農村部住民の血圧水準は、年齢を調整しても勤務者に比し収縮期血圧で約5.0 mmHg高かった。この要因の一つとして、塩分排泄量（摂取量）が、農村部住民は勤務者よりも3～4グラム高いことが考えられた。また、昔は都市部では総コレステロール値が高く、農村では低いことが常識であったが、今回の検討では、血清総コレステロール値はむしろ都市部勤務者でもっとも低く、農村部住民、地方勤務者でほぼ同等であった。集団における収縮期血圧の2 mmHgの差は、脳卒中死亡率における6 %の差をもたらすと、「健康日本21」の報告資料にもあるように(2)、数ミリの差でも循環器疾患の発症率や死亡率に大きな影響を与える。勤務者と農村部住民の間で他の危険因子に比し血圧の差が大きいという本研究の結果から、農村住民と勤務者の循環器疾患の危険因子に格差が存在するものとあまり存在しないものとが混在していることを示している。

血清総コレステロール値は、脂肪の摂取量、とりわけ、飽和脂肪酸と多価不飽和脂肪酸の摂取割合によって影響されることがよく知られている(3)。したがって、農村部住民の血清総コレステロール値が都市勤務者より高いということは、都市住民のほうが低飽和脂肪、高多価不飽和脂肪という健康的な脂肪摂取パターンを持っていることを示唆している。さらに一方では、以前、農村部の特徴であった塩分摂取量が多い傾向が、今も滋賀県の農村部住民には残っていることも明らかとなった。したがって農村部では、今後も高血圧対策の一環として減塩の取り組みが重要な課題であり、同時に食生活の欧米化について都市部以上に注意を払う必要があると思われる。また都市勤務者に比し、喫煙率が農村部住民および地方勤務者で高かったことは、今後の非都市的地域での喫煙対策の重要性を示している。喫煙により、循環器疾患発症と死亡率が高くなることはよく知られており(4)、喫煙対策を循環器疾患対策としても積極的に進めて行く必要がある。

本研究の重要な知見として、農村部の高血圧、糖尿病、高コレステロール血症等の服薬治療率は、

都市勤務者との間で大きな差はなく、地方勤務者よりもむしろ高かったことである。これは昨年の報告でも示したように、生活習慣の改善に関する項目、即ち、食事療法や運動療法の実施者の割合が、農村部住民と勤務者で大きく異なっていたためと考えられる。このことは、医療サービスを服薬治療という点に絞れば、地域差は解消しつつあるものの、保健サービス、即ち生活指導の面における格差が存在することを示唆していると考えられる。研究対象とした勤務者集団は、すべて東証一部上場の大企業の社員であり、地域住民に比し、社内の資源（産業医、産業看護職）を用いて生活習慣の改善指導等を受けやすいより恵まれた環境にあると思われる。また、勤務者集団は、もともと健康な労働者が働いているという選択バイアスもこの結果に影響を与えている可能性があり、ここで示した結果は、地域差というよりも“老人保健法を主体とした地域保健”と“労働安全衛生法を主体とした産業保健”の受益者の特性を反映しているのかもしれない。

しかし、いずれにしても、農村部住民における服薬治療などの純医療行為以外の保健サービスの提供体制は、都市部の事業所集団に比し劣っている可能性があり、今後、この面での改善が必要であるとの結論に変わりはない。現在、個別健康教育など地域での生活習慣病対策が実施されているが、参加率の伸び悩みや住民への浸透度の困難さという地域保健特有の問題もあり、その点を含めて抜本的な対策が必要である。現在、平成20年度の医療制度改革に伴い現行の地域住民を対象とした健診制度には大きな変革があると予想され、この格差を解消していくような取り組みが望まれる。特に食事療法や運動療法などの“生活習慣の改善”を農村部住民に浸透させていく仕組みが必要である。

文献

1. NIPPON DATA Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14year follow-up of randomly selected population from Japanese - Nippon DATA80. J Hum Hypertens 2003; 17:851-857.
2. 健康日本21企画検討委員会・健康日本21計画策定検討会報告書. 健康日本21. 21世紀における国民健康づくり運動について、財団法人　健康体力づくり事業財団、2000年.
3. 上島弘嗣、岡山　明編著. コレステロールを下げる健康教育. 新しいプログラムの手引き. 保健同人社、東京、2000.
4. Ueshima H, Choudhury SR, Okayama A, et al. Cigarette smoking as a risk factor for stroke death in Japan. NIPPON DATA80. Stroke 2004;35:1836-1841.

四　部

研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kanda H , Kita Y , Ueshima H, et al.	What factors are associated with high plasma B-type natriuretic peptide levels in a general Japanese population?	Journal of Human Hypertention	19	165-172	2005
Matsui K, Kita Y, Ueshima H.	Informed Consent, Participation in, and Withdrawal from a Population-based Cohort Study Involving Genetic analysis	J Med Ethics	31	385-392	2005
田中太一郎、岡村智教、上島弘嗣、他	事業所勤務者における高コレステロール血症の認識（awareness）・治療・コントロール状況（HIPOP-OHP study）	日本疫学会雑誌	15(suppl)	195	2005
井手真美、上島弘嗣、他	青・壮年者を対象とした生活習慣病予防のための長期介入研究（第 12 報）－弁当給食への介入－	栄養学雑誌	62(suppl)	215	2004
多田賢代、上島弘嗣、他	青・壮年者を対象とした生活習慣病予防のための長期介入研究（第 13 報）－4 年の介入経過－	栄養学雑誌	62(suppl)	215	2004
Saito I, Okamura T, Fukuhara S, Tanaka T, Suzukamo Y, Okayama A, Ueshima H and the HIPOP-OHP Research Group	A cross-sectional study of alcohol drinking and health-related quality of life among male workers in Japan.	J Occup Health	47(6)	496-503	2005
岡村智教、田中太一郎、武林亨、菊池有利子、由田克士、喜多義邦、三浦克之、上島弘嗣、中川秀昭	働き盛りの農村住民、都市部勤務者の循環器疾患危険因子の比較研究	日本公衆衛生雑誌（特別付録）	52 (8)	607	2005

五　部

研究成果の刊行物・別刷

Journal of Human Hypertension (2005) 19, 165–172

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ORIGINAL ARTICLE

What factors are associated with high plasma B-type natriuretic peptide levels in a general Japanese population?

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There are few community-based epidemiologic studies that have dealt with risk factors for heart failure in non-Western populations. It has been reported that the measurement of plasma B-type natriuretic peptide (BNP) is useful for detecting patients with asymptomatic heart failure. To clarify the determinants of high plasma BNP level, the association of BNP with cardiovascular risk factors in community dwelling residents was examined. The plasma BNP levels were measured in 686 residents aged 35–69 years who received annual health check-up. The relationship of BNP to blood pressure, blood haemoglobin, serum cholesterol (total and high-density lipoprotein cholesterol), plasma glucose, electrocardiographic (ECG) findings, urinary salt excretion, and lifestyle factors (smoking and alcohol consumption) were cross-sectionally analysed. The plasma BNP geometric mean was 13.7 pg/ml. Both linear and logistic regression analyses indicated that the plasma BNP levels were positively associated with age, urinary salt excretion, higher blood pressure, high R-wave voltage in the 12-lead ECG (Minnesota Code 3-1 or 3-3), and female gender. Plasma BNP levels were inversely associated with blood haemoglobin levels. Gender-specific analysis showed similar results. However, plasma BNP did not correlate with other cardiovascular risk factors such as serum lipids.
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Keywords: B-type natriuretic peptide; risk factors; urinary salt excretion; high R-wave voltage in the 12-lead ECG; general population

Introduction

Approximately 15% of deaths in Japan are due to heart diseases, of which about one-third are due to heart failure.[1] In 2001, mortality due to heart failure was 36.9 per 100 000 person-years, which is approximately two-thirds of that due to coronary heart disease (56.4 per 100 000 person-years).[1] The risk factors for coronary heart disease have been well described in several epidemiologic studies in Japan.[2–6] However, there are few available epidemiologic studies that deal with the risk factors for heart failure, even though it is a major problem in the Japanese population.[7,8] Accordingly, it is very important to clarify the risk factors for heart failure in Japan.

Congestive heart failure is usually regarded as the end-stage of the progressive deterioration of left ventricular function, which cannot be compensated for by cardiovascular homeostatic mechanisms.[9,10] Although heart failure is usually progressive, it can remain asymptomatic for many years. Thus, it would be of benefit to identify latent patients who have asymptomatic left ventricular dysfunction. However, in the general population, it is difficult and expensive in the primary care setting to screen the general population using Doppler echocardiography or exercise tolerance tests to diagnose left ventricular dysfunction.

B-type natriuretic peptide (BNP) is synthesized and released from the myocardium in response to an increase in ventricular filling pressure.[11] Recently, it was reported that the measurement of plasma BNP has a high sensitivity and a high specificity for detecting patients with asymptomatic heart failure or left ventricular dysfunction.[12–15] However, there are only a few studies that have examined the factors that are associated with high plasma BNP levels in the non-Western population.[16,17]

The purpose of this study is to clarify the risk factors for high plasma BNP levels, which is an important marker of asymptomatic heart failure, in a Japanese general population.

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Population and methods

Study population

The participants were 957 residents aged 35–69 years, who received regular annual health check-ups for the residents except for employees under the Health and Medical Service Law for the Aged, in SA town, Shiga Prefecture, a rural community in Western Japan. Well-trained nurses interviewed each participant to obtain a medical history and lifestyle information such as smoking and alcohol consumption. Of the 827 participants who gave informed consent, 13 participants did not have the complete data needed for the analysis. Of a total of 814 eligible participants, 128 were excluded for the following reasons: past or present history of coronary heart disease ($n=18$), diabetes mellitus ($n=48$), atrial fibrillation ($n=2$), and having symptoms suspected of heart failure, such as some clinical conditions that preclude physical exercise ($n=60$). No participants had a past or present history of renal disease. Thus, 686 residents aged 35–69 years participated in the study (209 men and 477 women; mean age $\pm$ s.d., 56.1 ± 9.7 years).

All the procedures of this study were reviewed and approved by the Institutional Review Board of Shiga University of Medical Science (No.14-10, 2002).

Clinical examination

The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). The blood pressure was measured twice after 5 min of rest using an automatic sphygmomanometer (COLIN CORPORATION, BP-103i II, Aichi, Japan) placed on the right arm of participants in the sitting position. The mean of the two measurements was used for this analysis. The blood pressure was classified into the following four categories using WHO criteria of 1999:[18] optimal and normal—systolic blood pressure (SBP) under 130 mmHg and diastolic blood pressure (DBP) under 85 mmHg; high normal—SBP 130–139 mmHg and/or DBP 85–89 mmHg; grade 1—SBP 140–159 mmHg and/or DBP 90–99 mmHg; and grades 2 and 3—SBP 160 mmHg or greater and/or DBP 100 mmHg or greater.

Blood samples were drawn from an antecubital vein of nonfasting participants, and then analysed in one laboratory (KINKIYOKEN, Shiga). Plasma samples for the BNP measurements were transferred immediately to tubes with 1.0 mg/ml of EDTA-2Na and 500 kallikrein inhibitory units (KIU)/ml of aprotinin. Plasma was obtained by centrifugation at 3000 rpm for 10 min at 4°C and stored at −80°C until analysis. Plasma BNP concentration was measured with specific immunoradiometric assays for human BNP (ShionoRIA BNP kit, Shionogi & Co., Ltd, Osaka, Japan).[12–14,16,19,20] For BNP, the intra- and inter-assay coefficients of variation for this assay were 1.3 and 3.2%, respectively. Plasma BNP level of 18 pg/ml or greater were considered indicative of potential left ventricular dysfunction. This was based on a previous study conducted in the UK that showed this BNP cutoff value had a sensitivity of 77% and a specificity of 87% in 1252 participants aged 25–74 years for diagnosing left ventricular systolic dysfunction (left ventricular ejection fraction 30% or less).[15]

Total cholesterol and high-density lipoprotein (HDL) cholesterol in serum were measured enzymatically. Lipid measurement at the reporting laboratory has been standardized at the Osaka Medical Center for Health Science and Promotion, by a member of the Cholesterol Reference Method Laboratory Network (CRMLN).[21,22] Plasma glucose was measured by the hexokinase method. Blood haemoglobin was determined by the latex coagulation method.

Electrocardiography (ECG) was performed by standard 12-lead ECG after the patient had rested sufficiently. Findings of high R-wave voltage, ST-T depression, and an inverse- or flat-T-wave in the ECG were defined according to the Minnesota Code (MC).[23] High R-wave voltage in the 12-lead ECG was defined by the following: an R-wave in V5 or V6 of 2.6 mV or greater (MC 3-1) and/or the height of the R-wave in V1 plus V5 or V6 of 3.5 mV or greater (MC 3-3). Other findings that were documented if present included ST-T depression (MC 4-1 or 4-3), and inverse or flat T-waves (MC 5-1 or 5-3).

Daily salt excretion was estimated by Tanaka's formulas,[24] which estimate populational daily urinary salt excretion from the sodium and creatinine levels in casual urine samples. Using a self-reported questionnaire administered by well-trained nurses, the participants were asked about daily alcohol intake and smoking habits.

Statistical analyses

The possible determinants of BNP were divided into quartiles or categories. Geometric means of BNP were used for the analysis of each determinant because the distribution of BNP was positively skewed. To compare these with the crude geometric means of BNP in each quartile or category, analysis of variance was used. Comparisons with age- and gender-adjusted geometric means of BNP were performed using analysis of covariance. Gender-specific analysis was also performed.

Linear regression analysis was used to clarify the contribution of each independent variable to BNP. Multiple logistic regression analysis was used to assess the contribution of each independent variable to a high plasma BNP level (18 pg/ml or greater). The significance of the interaction of sex with risk factors related to BNP was tested using an inter-

action term in multivariate models in the gender-combined analysis.

The Statistical Package for the Social Sciences (SPSS Japan Inc., version 11.0J, Tokyo, Japan) was used for the analyses. All probability values were two-tailed and all confidence intervals were estimated at the 95% level.

Results

Table 1 shows the means and the prevalence of risk factors. The mean plasma BNP was 13.7 pg/ml in the entire population, 10.7 pg/ml in men and 15.3 pg/ml in women.

There was no relationship between BNP level and each quartile for BMI, DBP, total cholesterol, HDL cholesterol, plasma glucose, and current smoking. Table 2 shows the geometric means of BNP according to the quartiles or categories (blood pressure category, high R-wave voltage, and current alcohol consumption) for each risk factor that was statistically significant in the analysis of variance or covariance. SBP, Grade 2 or severe hypertension category (SBP$\geqslant$160 mmHg and/or DBP$\geqslant$100 mmHg), high R-wave voltage in the ECG, and daily salt excretion were positively associated with BNP, and their values were higher in the higher BNP quartiles. There was a statistically significant relationship between the BNP levels and haemoglobin quartiles, with higher BNP levels in patients with haemoglobin values in the lower quartiles.

Since the interaction term between sex and risk factors related to BNP was not statistically significant in the multivariate regression analyses,

Table 1 Levels and prevalence of risk characteristics for males, females, combined among 686 subjects aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Males (n=209)*	*Females (n=477)*	*Combined (n=686)*
	mean±s.d.	*mean±s.d.*	*mean±s.d.*
Age (years)	57.1±9.1	55.6±9.9	56.1±9.7
Body mass index (kg/m)	23.8±2.9	23.0±3.0	23.3±3.0
Systolic blood pressure (mmHg)	130.1±18.0	124.0±18.3	125.8±18.4
Diastolic blood pressure (mmHg)	82.4±11.1	75.5±11.1	77.6±11.5
Total cholesterol (mmol/l)	5.29±0.79	5.59±0.91	5.50±0.89
High density lipoprotein (HDL) cholesterol (mmol/l)	1.39±0.38	1.63±0.39	1.56±0.40
Plasma glucose (mmol/l)	5.31±0.77	5.07±0.50	5.15±0.60
Haemoglobin (g/dl)	14.7±1.0	12.9±1.1	13.5±1.4
Salt excretion (g/day, estimated)	12.6±3.4	12.1±3.3	12.3±3.3
B type natriuretic peptide (BNP) (pg/ml, geometric mean)	10.7	15.3	13.7
	Prevalence (%)	*Prevalence (%)*	*Prevalence (%)*
ECG findings			
High R-wave voltage[a]	13.4	5.9	8.0
ST-depression[b]	0.0	1.9	1.3
Inverse or flat T-wave[c]	1.4	2.1	1.9
Blood pressure category[d]			
Optimal+normal	47.4	62.5	57.9
High–normal	16.3	14.5	15.0
Grade 1	27.8	17.6	20.7
Grade 2+3	8.6	5.5	6.4
Subject using antihypertensive agents	14.4	14.7	14.6
Smoking habit			
Nonsmoker	24.4	91.8	71.3
Ex smoker	23.4	1.9	8.5
Current smoker	52.2	6.3	20.3
Alcohol consumption			
Nondrinker	22.5	76.7	60.2
Ex drinker	1.0	0.4	0.6
Current drinker	76.6	22.9	39.2
Menopause	—	69.0	—
High plasma BNP (18 pg/ml or greater)	24.4	43.2	37.5

[a]High R-wave voltage:high R criteria:V5 or V6>2.6 mV, and/or V1 and V5 or V6>3.5 mV.
[b]ST-depression: the criteria for ST depression was the Minnesota Code 4-1 or 4-3.
[c]Inverse- or flat-T-wave: the criteria for inverse- or flat-T was the Minnesota Code 5-1 or 5-3.
[d]Blood pressure category: Optimal+normal: SBP<130 mmHg and DBP<85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1:SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP$\geqslant$160 mmHg and/or DBP$\geqslant$100 mmHg.

Table 2 Plasma BNP levels and quintiles for proportional variables among 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Number of subjects*	*Crude geometric mean (pg/ml)*	P*	*Age- and gender-adjusted geometric mean (pg/ml)*	P**
Systolic blood pressure (mmHg)					
Quartile 1 −111.3	171	12.7	0.004	13.6	0.041
Quartile 2 111.4–123.4	170	13.0		13.3	
Quartile 3 123.5–138.9	169	12.9		12.5	
Quartile 4 139.0–	176	16.5		15.5	
Blood pressure category[a]					
Optimal+normal	397	12.7	0.001	13.2	0.047
High–normal	103	14.1		13.2	
Grade 1	142	15.0		14.6	
Grade 2+3	44	19.5		17.8	
Haemoglobin (g/dl)					
Quartile 1 −12.5	159	17.5	0.000	17.0	0.000
Quartile 2 12.6–13.3	168	15.6		15.2	
Quartile 3 13.4–14.2	175	13.6		13.2	
Quartile 4 14.3–	184	10.0		10.8	
High R-wave voltage in the ECG[b]					
−	631	13.3	0.000	13.3	0.000
+	55	20.3		19.7	
Salt excretion (g/day, estimated)					
Quartile 1 −9.9	166	11.0	0.000	11.7	0.000
Quartile 2 10.0–11.8	171	12.3		12.3	
Quartile 3 11.9–13.9	171	15.7		15.1	
Quartile 4 14.0–	178	16.5		16.2	
Alcohol consumption					
Non-/ex drinker	417	14.4	0.037	13.1	0.053
Current drinker	269	12.7		14.8	

[a]Blood pressure category: Optimal+normal: SBP < 130 mmHg and DBP < 85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1: SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP ⩾ 160 mmHg and/or DBP ⩾ 100 mmHg.
[b]High R-wave voltage+high R criteria: V5 or V6 > 2.6 mV, and/or V1 and V5 or V6 > 3.5 mV.
*P: analysis of variance, **P: analysis of covariance.

the following analyses were carried out to combined men and women with adjustment for gender.

Table 3 shows the partial regression coefficients from the linear regression analysis. In this model, age, daily salt excretion, high R-wavé voltage, female gender, and SBP were positively associated with plasma BNP levels. Blood haemoglobin was negatively associated with BNP levels. The multiple correlation coefficient (R) of this model was 0.49 and the degrees of freedom (df)-adjusted coefficient of determination (R^2) was 0.23 ($F = 30.0$, $P < 0.001$). Alcohol consumption was positively associated with BNP levels, although it did not reach statistical significance ($P = 0.051$). BMI showed no association with BNP levels.

Table 4 shows the odds ratios of each risk factor with a high plasma BNP level (18 pg/ml or greater) determined using multiple logistic regression analysis. Age, daily salt excretion, high R-wave voltage, female gender, and grade 2 or greater hypertension were positively associated with high plasma BNP levels, and blood haemoglobin concentration was negatively associated. The significant relationship between BNP and salt excretion was also observed even after we excluded participants with high R-wave voltage or participants taking antihypertensive agents, although the relationship between BNP and SBP or hypertension disappeared when these patients were excluded.

Gender-specific analysis showed that plasma BNP levels were significantly correlated with age, urinary salt excretion, and low haemoglobin for each gender. We also observed positive relations of plasma BNP levels with SBP and high R-wave voltage for each gender, which indicated similar magnitude of regression coefficients or odds ratio, although the relation with SBP for women and high R-wave voltage for men did not reach statistical significance.

Further analysis adjusting for administration of antihypertensive agents, smoking, serum lipids, and plasma glucose did not substantially affect the results shown in Tables 3 (data not shown in the table).

Table 3 Determinants of plasma BNP levels: linear regression analysis, 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Partial regression coefficients*	*s.e.*[a]	t	P
Age (10 years)	0.210	0.029	7.296	0.000
Haemoglobin (1 s.d., 1.36 g/dl)	−0.196	0.034	−5.681	0.000
Salt excretion (1 s.d., 3.4 g/day)	0.133	0.027	4.892	0.000
High R-wave voltage in the ECG (0 = no, 1 = yes)[b]	0.325	0.098	3.326	0.001
Gender (0 = male, 1 = female)	0.251	0.080	3.140	0.000
Systolic blood pressure (1 s.d., 18.4 mmHg)	0.070	0.029	2.454	0.014
Alcohol consumption (0 = non- or ex drinker, 1 = current drinker)	0.123	0.062	1.987	0.051
Body mass index (1 s.d., 3.0 kg/m^2)	−0.021	0.028	−0.759	0.448

[a]Standard error.
[b]High R-wave voltage was defined by height of R-wave in the ECG ;V5 or V6 is 2.6 mV or greater, and/or height of R-wave for V1 plus V5 or V6 is 3.5 mV or greater.

Table 4 Multivariate odds ratio and 95% confidence intervals for having high plasma BNP (⩾18.0 pg/ml), 686 males and females aged 35–69 years old in SA-Town, Shiga, Japan, 2002

Variables	*Odds ratio*	*95% confidence interval*		
Age (years)	1.05	1.03	—	1.07
Haemoglobin (g/dl)	0.69	0.58	—	0.81
Salt excretion (g/day)	1.09	1.03	—	1.15
High R-wave voltage in the ECG (0 = no, 1 = yes)[a]	2.05	1.10	—	3.81
Gender (0 = male, 1 = female)	2.01	1.18	—	3.41
Blood pressure category[b]				
Optimal+normal	1.00		—	
High–normal	0.92	0.56	—	1.51
Grade 1	1.28	0.82	—	2.01
Grade 2+3	2.09	1.04	—	4.22
Alcohol consumption (0 = non- or ex drinker, 1 = current drinker)	1.45	0.97	—	2.17
Body mass index (kg/m^2)	0.99	0.93	—	1.06

[a]High R-wave voltage was defined by height of R-wave in the ECG; V5 or V6 is 2.6 mV or greater, and/or height of R-wave for V1 plus V5 or V6 is 3.5 mV or greater.
[b]Blood pressure category: Optimal+normal: SBP < 130 mmHg and DBP < 85 mmHg, high–normal: SBP 130–139 mmHg and/or DBP 85–89 mmHg, grade 1: SBP 140–159 mmHg and/or DBP 90–99 mmHg, grade 2+3: SBP ⩾ 160 mmHg and/or DBP ⩾ 100 mmHg.

Discussion

The present study suggests that higher blood pressure, urinary salt excretion (a surrogate measure of dietary salt intake), high R-wave voltage in the ECG, and low blood haemoglobin as well as age and female gender are important determinants of plasma BNP levels in a general Japanese population.

Previous studies have reported a positive relationship between heart failure and hypertension.[19,25] The present study has also shown a positive relationship between grade 2 or greater hypertension and high levels of plasma BNP. Similar to previous reports dealing with Western populations, hypertension of moderate or greater degree may be one of the risk factors for asymptomatic heart failure or left ventricular dysfunction in the Japanese population. Hypertension, which is derived mainly from increased systemic vascular resistance and/or expanded intravascular volume, causes a sustained increase in left ventricular afterload that decreases cardiac output or ejection fraction, ultimately resulting in congestive heart failure.[19]

In general, urinary salt excretion is nearly equal to the dietary salt intake. High salt intake is an important factor that can expand intravascular volume, and it is a major causal risk factor for hypertension.[26–29] A recent study suggested that high salt intake *per se*, independent of hypertension, can have a harmful effect on the general population owing to the high risk of total mortality and mortality due to coronary heart disease and stroke.[30,31] A previous study reported that chronic high dietary salt intake increases the plasma concentration of BNP, even in the absence of hypertension.[32] It has also been reported that high dietary salt intake is related to the incidence of congestive heart failure in overweight men and women in the United States.[20] Furthermore, it has been emphasized that high salt intake is a risk factor for left ventricular hypertrophy.[33–35] High salt intake may be directly correlated to plasma BNP concen-

tration due to an increase in the circulating blood volume, which may indirectly lead to an increase in myocardial mass due to hypertension. The relationship between BNP and daily salt excretion was present after exclusion of subjects taking antihypertensive agents or those who had high R-wave voltage.

BNP, as a cardioprotective factor, has a diuretic effect that promotes the excretion of water and sodium by the kidneys.[36,37] As a result of the high sodium excretion promoted by BNP, the amount of urinary salt excretion may overestimate the actual dietary salt intake in participants with high plasma BNP levels. However, participants with high urinary salt excretion are continually exposed to high salt intake, which results in a situation that high BNP secretion is needed in order to protect their circulatory system. Consequently, we believe that a high salt intake may be a causal risk factor for heart failure or left ventricular dysfunction.

Left ventricular hypertrophy, which is usually accompanied by hypertension, is an example of target organ damage caused by an increase in circulating blood volume and/or vascular resistance occurring over many years. In the Framingham study, cardiac mass was assessed using echocardiography.[12] In the present study, we used the presence of high R-wave voltage in the 12-lead ECG as an index of left ventricular hypertrophy. An ECG is a more convenient and inexpensive method than an echocardiogram, and it is suitable for mass screening in the community. Moreover, people aged 40 years or greater in Japan are able to have an annual ECG under the Health and Medical Service Law for the Aged or the Industrial Safety and Health Law. In a previous study, significantly higher BNP levels were noted in patients with heart disease or hypertension who had abnormal electrocardiographic findings, such as high R-wave voltage.[38] Our finding seems to be consistent with this previous study, although our participants were healthy community dwelling residents.

Hypertension, high salt excretion, and high R-wave voltage in the ECG, which are associated with high BNP levels, are also the classical risk factors for stroke reported in previous Japanese cohort studies.[39–42] However, serum total cholesterol, which is a risk factor for ischaemic heart disease and not for stroke in Japan,[2–5] was not associated with plasma BNP levels. Since mortality due to ischaemic heart disease in Japan is lower than that in Western populations,[1,6,43] it may be reasonable to assume that the risk factors for latent heart failure are similar to those for stroke in the Japanese population.

Another interesting finding in the present study was the negative correlation between blood haemoglobin and BNP. It has been reported that anaemia is an independent prognostic factor for mortality in congestive heart failure patients living in the community.[44] Our result suggests that a low blood haemoglobin concentration, even within the clinically normal range, is associated with high plasma BNP. A reduced haemoglobin concentration might be a maker for advanced heart failure that may occur as a result of haemodilution due to volume overload and renal insufficiency.[44] Other factors in heart failure that are associated with anaemia include iron deficiency, chronic inflammation, and impaired erythropoietin production.[45]

Several limitations of this study should be acknowledged. First, we dealt with high R-wave voltage in the ECG as a marker for left ventricle hypertrophy, which may not always reflect true cardiac mass. Although body mass may affect R-wave amplitude, we statistically adjusted for the effect of body mass index. Unfortunately, due to the low prevalence of other abnormal findings in the ECG such as ST-T depression (1.3%) and inverse or flat T-waves (1.9%), we were not able to use these findings in our analysis. Second, our study used a cross-sectional design, which does not prove causal relations between plasma BNP levels and the above-mentioned risk factors.

In conclusion, we clarified the relationship between the elevated plasma BNP and hypertension, urinary salt excretion, high R-wave voltage in the ECG, age, and low haemoglobin concentration in a Japanese general population. We found some possible determinants for the elevation of plasma BNP in the Japanese general population. These factors — age, urinary salt excretion, hypertension — are similar to the classical risk factors for stroke in Japan.

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References

1 Statistics and Information Department. Ministry of Health and Welfare, Labor. *Vital Statistics of Japan 2001*. Health and Welfare Statistics Association: Tokyo, 2003, pp 390–391.
2 Shimamoto T *et al*. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989; **79**: 503–515.
3 Kiyohara Y, Ueda K, Fujishima M. Smoking and cardiovascular disease in the general population in Japan. *J Hypertens* 1990; **8**(Suppl): S9–S15.
4 Ueshima H. Changes in dietary habits, cardiovascular risk factors and mortality in Japan. *Acta Cardiol* 1989; **44**: 475–477.
5 Ueshima H, Tatara K, Asakura S. Declining mortality from ischemic heart disease and changes in coronary risk factors in Japan, 1956–1980. *Am J Epidemiol* 1987; **125**: 62–72.

6 Okamura T *et al.* What cause of mortality can we predict by cholesterol screening in the Japanese general population? *J Intern Med* 2003; **253**: 169–180.
7 Itoh A *et al.* Prognosis of patients with congestive heart failure: its determinants in various heart diseases in Japan. *Intern Med* 1992; **31**: 304–309.
8 Tsuchihashi M *et al.* Clinical characteristics and prognosis of hospitalized patients with congestive heart failure—a study in Fukuoka, Japan. *Jpn Circ J* 2000; **64**: 953–959.
9 McKee PA *et al.* The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971; **285**: 1441–1446.
10 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; **327**: 685–691.
11 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998; **339**: 321–328.
12 Wang TJ *et al.* Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002; **90**: 254–258.
13 Nakamura M *et al.* Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. *Heart* 2002; **87**: 131–135.
14 Vasan RS *et al.* Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. *JAMA* 2002; **288**: 1252–1259.
15 McDonagh TA *et al.* Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998; **351**: 9–13.
16 Kato J *et al.* Plasma levels of adrenomedullin and atrial and brain natriuretic peptides in the general population: their relations to age and pulse pressure. *Hypertens Res* 2002; **25**: 887–892.
17 Matsuda M. The significance of plasma BNP measurement in the health check up. *Kyorin Igakkai Zasshi* 1999; **30**: 73–83 (in Japanese).
18 WHO guideline subcommittee. 1999 World Health Organization—International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999; **17**: 151–179.
19 Strauer BE. Hypertension and the heart: clinical studies. In: Zanchetti A, Tarazi RC (eds). *Handbook of Hypertension*, Vol. 7. Elsevier: New York, 1986.
20 He J *et al.* Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Arch Intern Med* 2002; **162**: 1619–1624.
21 Myers GL *et al.* A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. *Clin Chem* 2000; **46**: 1762–1772.
22 Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003; **10**: 145–153.
23 Prineas RJ, Crow RS, Blackburn H. *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification.* John Wright-PSG Inc.: Litteleton, MA, 1982.
24 Tanaka T *et al.* A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. *J Hum Hypertens* 2002; **16**: 97–103.
25 Ghali JK *et al.* Precipitating factors leading to decompensation of heart failure. Traits among urban blacks. *Arch Intern Med* 1988; **148**: 2013–2016.
26 Jackson FL. An evolutionary perspective on salt, hypertension, and human genetic variability. *Hypertension* 1991; **17**(Suppl 1): 129–132.
27 Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? I: Analysis of observational data among populations. *BMJ* 1991; **302**: 811–815.
28 Midgley JP *et al.* Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1590–1597.
29 INTERSALT Co-operative Research Group. The INTERSALT study. *J Hum Hypertens* 1989; **3**: 279–331.
30 Tuomilehto J *et al.* Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 2001; **357**: 848–851.
31 Nagata C *et al.* Sodium intake and risk of death from stroke in Japanese men and women. *Stroke* 2004; **35**: 1543–1547.
32 Ishimitsu T *et al.* Responses of natriuretic peptides to acute and chronic salt loading in normotensive and hypertensive subjects. *Hypertens Res* 1998; **21**: 15–22.
33 Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994; **89**: 1041–1050.
34 Beil AH, Schmieder RE. Salt intake as a determinant of cardiac hypertrophy. *Blood Press* 1995; **2**(Suppl): 30–34.
35 Seta H *et al.* Analysis of factors influencing left ventricular mass and diastolic function in normotensive men. *J Cardiol* 2001; **37**: 249–256 (in Japanese).
36 Mukoyama M *et al.* Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. *J Clin Invest* 1991; **87**: 1402–1412.
37 Yasue H *et al.* Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994; **90**: 195–203.
38 Hirata Y *et al.* Measurement of plasma brain natriuretic peptide level as a guide for cardiac overload. *Cardiovasc Res* 2001; **51**: 585–591.
39 Tanaka H *et al.* Epidemiologic studies of stroke in Shibata, a Japanese provincial city: preliminary report on risk factors for cerebral infarction. *Stroke* 1985; **16**: 773–780.
40 Tanaka H *et al.* Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. *Stroke* 1982; **13**: 62–73.
41 Lin CH *et al.* Cerebrovascular diseases in a fixed population of Hiroshima and Nagasaki, with special reference to relationship between type and risk factors. *Stroke* 1984; **15**: 653–660.
42 Ueshima H *et al.* Multivariate analysis of risk factors for stroke. Eight-year follow-up study of farming villages in Akita, Japan. *Prev Med* 1980; **9**: 722–740.

43 Sekikawa A *et al.* A "natural experiment" in cardiovascular epidemiology in the early 21st century. *Heart* 2003; **89**: 255–257.
44 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003; **107**: 223–225.
45 Okonko DO, Anker SD. Anemia in chronic heart failure: pathogenetic mechanisms. *J Card Fail* 2004; **10**(Suppl 1): S5–S9.

GENETICS

Informed consent, participation in, and withdrawal from a population based cohort study involving genetic analysis

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Objective: Population based cohort studies involving genetic research have been initiated in several countries. However, research published to date provides little information on the willingness of the general population to participate in such studies. Furthermore, there is a need to discover the optimal methods for acquiring fully informed consent from the general population. We therefore examined the results of a population based genetic cohort study to identify the factors affecting the participation rate by members of the general public and also specifically to examine the impact of different consent procedures on the rate of participation by prospective candidates and their subsequent withdrawal rate from the study.
Design: Descriptive analyses.
Setting and participants: The study evaluated two non-genetic subcohorts comprising 3166 people attending for a health checkup during 2002, and two genetic subcohorts comprising 2195 people who underwent a checkup during 2003.
Main outcome measurements: Analysis endpoints were differences in participation rates between the non-genetic and genetic subcohorts, differences between providing non-extensive and extensive preliminary information, and changes in participation status between baseline and at 6 months.
Results: Participation rates in the genetic subcohorts were 4·7–9·3% lower than those in the non-genetic subcohorts. The odds ratios (OR) of participation in genetic research were between 0·60 and 0·77, and the OR for withdrawal from the research was over 7·70; providing preliminary extensive information about genetic research reduced the withdrawal risks (OR 0·15 for all dependent variables) but worsened participation rates (OR 0·63–0·74).
Conclusions: The general population responded sceptically towards genetic research. It is crucial that genetic researchers utilise an informative and educational consent process worthy of public trust.

Several studies have examined informed consent in connection with family based genetic testing and clinical genetic research.[1–3] However, because of the nature of the research, the participants in these studies primarily comprised patients, which could limit the applicability of the results to the general population. In particular, restricting recruitment for clinical genetic research studies to patients introduces a potential selection bias because their health status could cause them to be more motivated to participate in a research study compared with members of the general population.[4] Consequently, the clinical results and perspectives on informed consent of patient based genetic research studies are not necessarily representative of the opinions and attitudes of the general population regarding participation in population based genetic research.

Medical researchers have initiated large scale population based genetic cohort studies such as the Icelandic Health Sector Database and the UK Biobank[5 6] to obtain genetic information from large populations. Resistance or outright opposition to these studies[7 8] has arisen for the following reasons: concerns about misuse of genetic information or invasion of privacy; baseless fears of prospective participants concerning genetic studies; or simply an unwillingness among people to become involved with genetic research.

However, it remains poorly understood what the general population thinks of genetic research and how people are likely to respond when faced with a decision whether or not to participate in a genetic cohort study. Researchers have had great difficulty in reducing selection bias when they have tried to encourage members of the general population voluntarily to participate in surveys of public opinion about informed consent for population based genetic research. Furthermore, such surveys have had to rely on hypothetical or virtual questionnaires employing "if then" questions[9 10] such as: (1) If you were to imagine yourself as a prospective genetic research participant, would you then take part in such a study? or (2) If you were to imagine yourself as a patient suffering from a serious genetic disease with no established treatment, would you then be willing to participate in genetic research if you were asked to do so by your physician? The responses of people to such questions regarding participation in genetic research would thus be theoretical in nature. Actual responses regarding informed consent to genetic research obtained from the general population in real-life situations remain unknown.

To our knowledge, the present study represents the first investigation in a real-life setting of informed choice/consent by the general population regarding participation in a cohort study involving genetic research. We performed statistical analyses of data from the Takashima study, the first Japanese population based genetic cohort study, to determine differences in participation rates between members of its non-genetic and genetic subcohorts. The cohorts differed from each other by the former donating only non-genetic samples while the latter donated non-genetic samples plus genetic material. Our statistical analyses also identified which methods of obtaining informed consent were more successful and in harmony with scientific and ethical values in persuading members of the general population to participate in this genetic cohort study.

PARTICIPANTS AND METHODS

This present study analyses data from the parent population based cohort study involving genetic research, the Takashima

study, part of the Japan arteriosclerosis longitudinal study.[11] Participants were drawn from two non-genetic subcohort areas, Adogawa and Shin-asahi, and two genetic subcohort areas, Takashima and Makino, in Takashima County, Shiga, Japan.

Demographic characteristics of the subcohorts

Table 1 shows the characteristics of the four subcohort areas in the Takashima study; all data are based on the 2000 population census of Japan.[12] All are mountainous rural areas in central Japan with ageing homogeneous populations, classified culturally into the same subgroup, and with similar standards of living.

Participants

Participants in the Takashima study were recruited from residents aged 18 years and over who took part in the annual health checkup programme provided under the Health and Medical Service Law for the Aged[13] during 2002 in Adogawa and Shin-asahi, and during 2003 in Takashima and Makino. A total of 2232 people took part in the health check programme in Adogawa, 957 in Shin-asahi, 1117 in Takashima, and 1162 in Makino (table 2).

The Takashima study, which began in 2002, is investigating onset factors of lifestyle related diseases, including stroke, myocardial infarction, heart failure, cancer, and dementia. It comprises a 3-year baseline survey plus a 20-year follow-up period.

During informed consent procedures for the Takashima study, those who appeared to be incompetent and who intentionally avoided the negotiations were excluded from further study. Consequently, of all participants in the health checkup programme, 2213 (99·1%) people in Adogawa, 953 (99·6%) in Shin-asahi, 1065 (95·3%) in Takashima, and 1130 (97·2%) in Makino gave informed consent (table 2). All interviews concerning informed consent were performed in accordance with a predefined protocol by researchers, physicians, nurses, and public health nurses.

This descriptive study and the Takashima study were reviewed and approved by the institutional review board of Shiga University of Medical Science as well as by the four municipalities in which the study participants resided.

Preliminary information provided in the cohort study and consent

Two designs were used for the Takashima study, which were based on research year. These had different methods of giving participants preliminary information about the study. Design 1 used method 1; design 2 used method 2-1 or method 2-2, between which there were differences with respect to the amount of information given.

Design 1

The 2002 study in Adogawa and Shin-asahi was a "basic survey". In addition to the full blood count, standard blood chemistry tests, and urinalysis designated by the health checkup programme, participants in the cohort study received additional blood chemistry tests, additional urinalysis, and answered a questionnaire about nutrition and physical activities. No genetic research was conducted.

Design 2

The 2003 study carried out in Takashima and Makino consisted of a "genetic analysis" involving extraction and further analyses of DNA, plus the basic survey and the health checkup programme.

Method 1: standard information methods applied in non-genetic subcohorts

Methods used to inform the participants in Adogawa and Shin-asahi about the Takashima study included the following: (1) sending out notices about the study; (2) distributing explanatory documents about the study in advance; and (3) providing oral explanations at each checkup site before consent was given. (These methods of providing preliminary information are commonly used together in Japanese

Table 1 Characteristics of the total populations from which the study subcohort samples were obtained (data from the 2000 Population Census of Japan[12])

	Adogawa	Shin-asahi	Takashima	Makino
Population				
Total	14 489	11 068	7 138	6 210
Men (%)	5 397 (48·8)	3 377 (47·3)	2 982 (48·0)	
Women (%)	5 671 (51·2)	3 761 (52·7)	3 228 (52·0)	
Population density (per hectare)				
No. people	2·98	3·37	0·79	1·12
No. people per dwellable area	5·23	5·75	4·11	3·18
Households				
Total number	4 413	3 310	2 032	1 873
Mean no. family members per household	3·28	3·34	3·51	3·31
Age (years)*				
⩽14 (%)	1 897 (17·1)	1 076 (15·1)	916 (14·8)	
15–64 (%)	8 965 (61·9)	6 979 (63·1)	4 353 (61·0)	3 729 (60·0)
⩾65 (%)	3 180 (21·9)	2 192 (19·8)	1 709 (23·9)	1 564 (25·1)
Industrial population				
Primary† (%)	556 (7·6)	254 (4·5)	261 (7·6)	253 (8·1)
Secondary‡ (%)	2 876 (39·5)	2 700 (47·1)	1 214 (35·2)	1 380 (44·4)
Tertiary¶ (%)	3 857 (52·9)	2 775 (48·4)	1 969 (57·2)	1 472 (47·4)
Total	7 289	5 729	3 444	3 105
NHI membership§				
% total population	38·69	36·37	35·81	37·57

*Adogawa 7 missing records, Makino 1 missing record.
†Agriculture, fishing, forestry etc.
‡Manual labour.
¶Service industry.
§NHI, Japanese National Health Insurance programme. This health insurance system is compulsory for everyone living in Japan and is divided into two categories. One is for employees and their dependents (Employees' Health Insurance Programme); the other is for farmers, self-employed people, pensioners, and their dependents (National Health Insurance Programme), which covers about 35% of the population.

Table 2 Numbers taking part in the annual health checkup programme, and research participants who gave informed consent during 2002–2003

	Basic survey						Basic survey + genetic analysis						
	Adogawa			Shin-asahi			Takashima			Makino			
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	p value (2-tailed)
No. taking part in annual health checkup programme* (%)	2232	822 (36·8)	1410 (63·2)	957	278 (29·0)	679 (71·0)	1117	361 (32·3)	756 (67·7)	1162	455 (39·2)	707 (60·9)	<0·0001
No. participants giving informed consent (% participation)	2213 (99·1)	812 (98·8)	1401 (99·4)	953 (99·6)	277 (99·6)	676 (99·6)	1065 (95·3)	344 (95·3)	721 (95·4)	1130 (97·2)	438 (96·3)	692 (97·9)	<0·0001
Age (years): no. (%)													
18–29		0 (0·0)	0 (0·0)		0 (0·0)	0 (0·0)		0 (0·0)	0 (0·0)		24 (5·5)	37 (5·3)	
30–39		41 (5·0)	154 (11·0)		10 (3·6)	70 (10·4)		20 (5·8)	69 (9·6)		32 (7·3)	81 (11·7)	
40–49		57 (7·0)	186 (13·3)		43 (15·5)	102 (15·1)		19 (5·5)	91 (12·6)		26 (5·9)	86 (12·4)	
50–59		134 (16·5)	277 (19·8)		74 (26·7)	202 (29·9)		50 (14·5)	118 (16·4)		79 (18·0)	169 (24·4)	
60–69		267 (32·9)	446 (31·8)		150 (54·2)	302 (44·7)		103 (29·9)	216 (30·0)		154 (35·2)	192 (27·7)	
70–79		270 (33·3)	300 (21·4)		0 (0·0)	0 (0·0)		137 (39·8)	195 (27·0)		109 (24·9)	110 (15·9)	
≥80		43 (5·3)	38 (2·7)		0 (0·0)	0 (0·0)		15 (4·7)	32 (4·4)		14 (3·2)	17 (2·5)	
Mean age (SD)		64·2 (12·0)	59·1 (13·1)		58·1 (9·0)	55·7 (10·1)		64·8 (12·0)	60·7 (13·3)		60·8 (14·5)	56·5 (14·6)	

*The annual health checkup programme in Japan has been provided to residents aged 18 years and over under the Health and Medical Service Law for the Aged[13] since 1982.

epidemiological surveys.) After the consent session, participants gave written consent if they understood the purposes and methods of the study, and if they agreed voluntarily to participate. The consent items were:

- Item 1: Do you agree or disagree to participate in the basic survey?
- Item 2: Do you agree or disagree to let your blood samples be preserved for future use?
- Item 3: Do you agree or disagree to allow this study's researchers to examine your medical records and your death certificate?

Participants then ticked "I agree" or "I disagree" for each item, and signed the consent form. They were also given a form they could use later if they wished to withdraw from any of their agreements to the study.

Method 2-1: standard information methods applied in the Takashima genetic subcohort

Method 1 was used in Takashima, with the addition to the written and oral explanations of details about genetic analysis. Thus, two additional consent items for genetic analysis were added:

- Item 4: Do you agree or disagree to participate in genetic analysis?
- Item 5: Do you agree or disagree to let your DNA samples be preserved for future analysis?

Method 2-2: extensive information methods applied in the Makino genetic subcohort

In addition to Method 2-1, we conducted, in advance, lectures at Makino town hall on clinical aspects related to genes and lifestyle related diseases, and we explained the nature of our genetic research. Furthermore, we held many explanatory meetings in all administrative districts to enable prospective participants to understand the study better.

Statistical methods

Comparisons of the rates of participation in and withdrawal from each consent item were performed between the four subcohort areas according to the differences in the respective designs and methods used. A 2-tailed χ^2 test and multiple logistic regression analyses were used. For the regression analyses, Adogawa (control group) and Shin-asahi, Adogawa (control) and Takashima, and Takashima (control) and Makino were compared respectively to calculate the odds ratios for the following:[14] (1) the demographic characteristics of the study areas; (2) the implementation of genetic analysis; and (3) the implementation of methods of giving extensive preliminary information about the study. For these analyses, participation rate and withdrawal rate were the dependent variables; and age, gender and items 1–3 above were the independent variables. We used SPSS (version 11·0J) for the statistical analysis. The investigators had full access to all the data and performed the analyses without restriction or limitation from the sponsors.

RESULTS

Crude participation rates at baseline and after 6 months

Table 3 presents the crude participation rates at baseline and 6 months after the baseline survey, excluding withdrawals, with respect to each consent item in the four subcohorts.