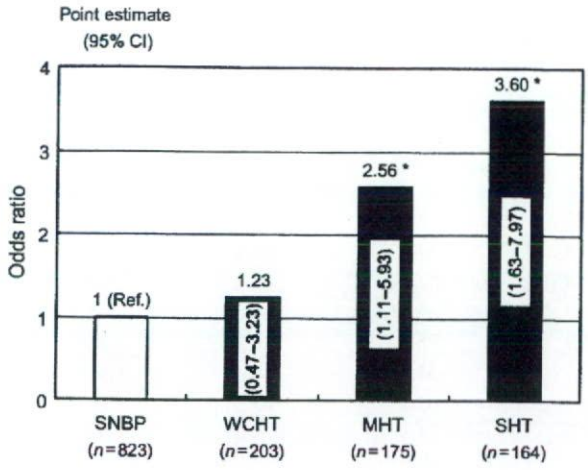

Fig. 1. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr<60 mL/min with proteinuria in the four groups. This figure shows the values of the four groups classified by blood pressure threshold. Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p<0.05 (maximum likelihood estimates).*

Results

The mean age of the 1,365 subjects was 63.0±8.9 years, and 32.5% were male. The mean BMI was 23.4±3.1 kg/m^2. Ninety-two subjects (6.7%) had a positive test for urinary protein. The mean estimated CCr was 60.9±16.4 mL/min (range, 15.4–132.0). The average HBP was 124/75 mmHg and the average CBP was 130/72 mmHg. A total of 12.5% of subjects were classified as current smokers, 31.0% were treated with antihypertensive medication, and 5.3%, 10.4%, and 31.6% of subjects were classified as having a history of cardiovascular disease, diabetes mellitus, and hypercholesterolemia, respectively.

We obtained a total of 26.0±4.6 measurements for HBP in each subject in the present study. A total of 60.3% of subjects were classified as having SNBP, 14.9% were classified as having WCHT, 12.8% were classified as having MHT, and 12.0% were classified as having SHT. Characteristics of the respective groups are shown in Table 1. Mean estimated CCr was significantly lower in the MHT and SHT groups (59.6 and 57.3 mL/min, respectively) than in the SNBP group (61.7 mL/min). The prevalence of CCr<60 mL/min was significantly higher in the MHT and SHT groups (57.7% and 56.8%, respectively) than in the SNBP group (51.1%). The percentage of subjects with proteinuria was significantly higher in the MHT and SHT groups (10.3% and 12.8%, respectively) than in the SNBP group (4.2%). Moreover, the prevalence of CCr<60 mL/min with proteinuria was significantly higher in the MHT and SHT groups (6.3% and 9.8%, respectively) than in the SNBP group (2.3%). This significant difference in CCr and proteinuria was not observed between the SNBP and WCHT groups.

The adjusted odds ratios (ORs) calculated by multiple logistic regression for the subjects with CCr<60 mL/min and proteinuria in each of the four groups are shown in Fig. 1. The likelihood of having a CCr<60 mL/min and proteinuria was significantly higher for subjects in the MHT group (OR 2.56, 95% CI 1.11 to 5.93) and SHT group (OR 3.60, 95% CI 1.63 to 7.97) than in the SNBP group (Fig. 1). A similar trend was also observed irrespective of antihypertensive treatment: The likelihood of having a CCr<60 mL/min and proteinuria was significantly higher in the MHT and SHT groups, both with and without antihypertensive treatment (Fig. 2). On the other hand, the likelihood of having a CCr<60 mL/min and proteinuria was not significant for the WCHT group (Fig. 1), irrespective of the presence of antihypertensive treatment (Fig. 2). HBP and CBP values were significantly correlated ($p<0.0001$, $r^2=0.26$).

We also evaluated the OR for the subjects with CCr<60 mL/min and proteinuria using the data of 2-d HBP values, which were calculated using the same number of measurements as the CBP, and observed a similar trend (Figs. 3 and 4). The 2-d HBP and CBP values were significantly correlated ($p<0.0001$, $r^2=0.21$).

Discussion

This community-based study demonstrated that MHT and SHT are closely associated with CKD in the Japanese general population and that there is a significantly higher probability of CKD in these hypertension types compared with SNBP or WCHT subjects. To our knowledge, this is the first report to suggest the clinical significance of MHT for CKD in a community-based cohort.

GFR decline is closely related to poor volume control and is linked with an elevation of oxidative stress, a non-traditional CVD risk (*19*). On the other hand, proteinuria, which is a risk of GFR decline (*20*) and cardiovascular events (*21*), is a marker of endothelial cell dysfunction or systemic vasculopathy (*22*). Based on this medical background information, it has been speculated that decreased GFR with proteinuria may exaggerate the risk of CVD events and poor patient outcomes. A recent report by Irie *et al.* suggested that the combination of proteinuria and hypercreatininemia or reduced GFR was a significant predictor of CVD and overall mortality (*23*).

In the present study, subjects with MHT and SHT, but not those with WCHT, were revealed to have this condition at a higher prevalence. Furthermore, the odds of having CCr<60 mL/min with proteinuria in the MHT and SHT groups were significantly higher than in the SNBP group, irrespective of

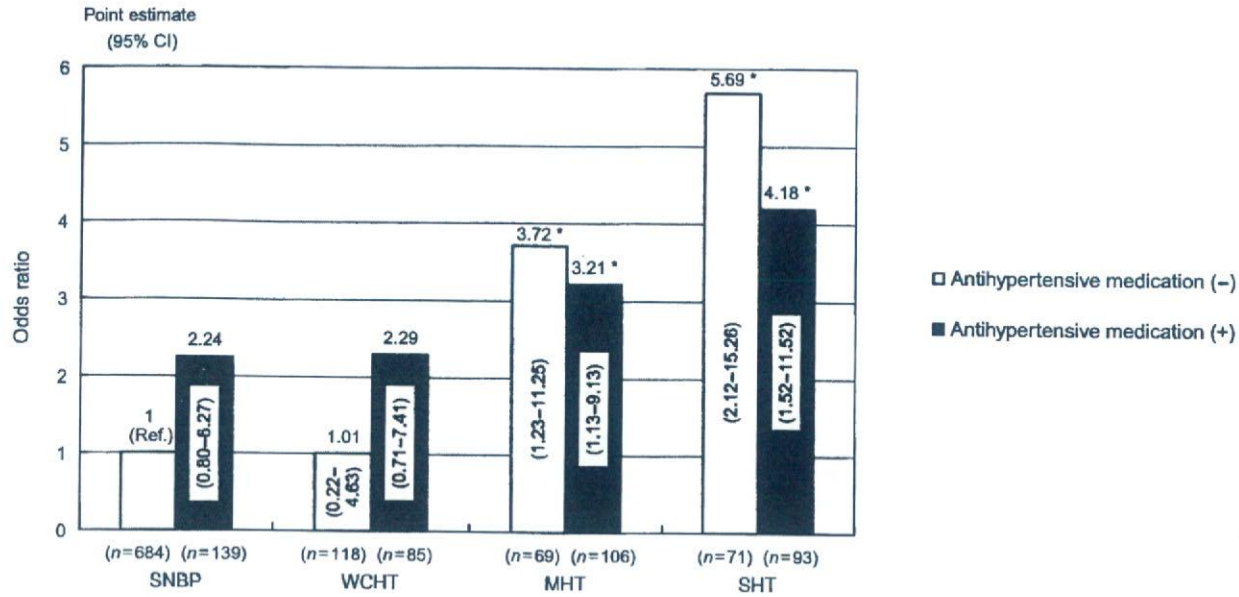

Fig. 2. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the presence or absence of antihypertensive medication. Participants were further divided into eight groups according to blood pressure threshold and the presence or absence of antihypertensive medication (each p value for interaction was > 0.14). Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

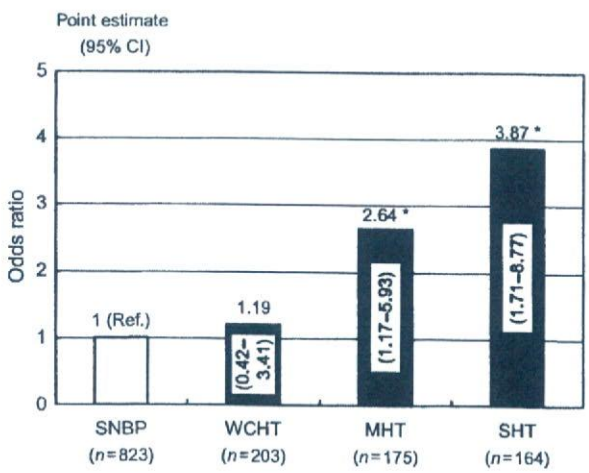

Fig. 3. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the four groups classified on the basis of 2-d HBP values. Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

the use of antihypertensive medications. These results suggest that, in addition to CBP, identification of MHT through the use of HBP could be an important screening strategy in the detection of CKD subjects.

The finding of the superior predictive value of HBP compared with CBP for CKD (Fig. 1) may be biased due to the method of the present study. We employed multiple measurements of HBP and a limited number of measurements of CBP (twice), which might have contributed to the results (Fig. 1). Therefore, we performed further analyses using the same number of measurements for HBP as for CBP (two measurements) and confirmed that HBP had retained a stronger predictive power than CBP (Fig. 3). In light of this, it is suggested that factors other than the number of measurements, such as the lack of the white-coat effect and the timing of BP measurement in the early morning, might be associated with the superior predictive power of HBP. With regard to the timing of BP measurements early in the morning, the effect of antihypertensive treatment should be considered, because a third of the study participants were regular users of antihypertensive medication. It is likely that the early-morning HBP of participants on antihypertensive treatment was affected by an insufficient duration of action of the antihypertensive drugs. Because the trough/peak ratios of most antihypertensive drugs are reported to be <50% (*24*), poor BP control late at night and early in the morning could be overlooked in BP

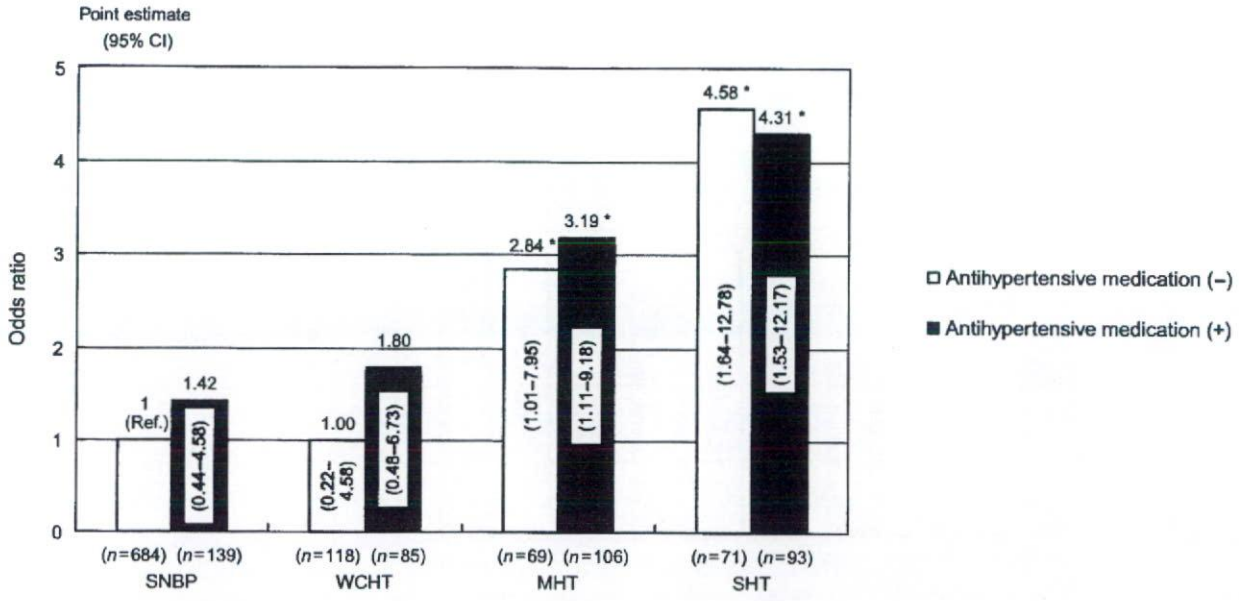

Fig. 4. *Odds ratios (ORs) and 95% confidence intervals for the presence of CCr < 60 mL/min with proteinuria in the presence or absence of antihypertensive medication based on 2-d HBP values. The eight groups were classified on the basis of 2-d HBP values (each p value for interaction was > 0.63). Values were adjusted for age, gender, body mass index, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension. *p < 0.05 (maximum likelihood estimates).*

measurements performed in the daytime (office BP measurement). This could be a reason why the OR of CKD risk is higher in the MHT group than in the WCHT group.

Recently, Agarwal and Andersen showed that HBP is a stronger predictor than CBP of progression to end-stage renal failure and mortality in CKD patients (*25*). Taking this finding together with our findings, control of HBP could be a therapeutic target in patients with CKD in terms of prevention of CVD events in CKD. This important issue could be a clinical challenge and should be addressed in future.

There are some limitations in this study. The first limitation involves the method of estimating renal function. We could not employ the recently recommended isotope dilution mass spectrometry–derived new modification of diet renal disease study (MDRD) equation to predict the estimated GFR (*26*) because serum creatinine levels were measured by the Jaffe assay and the accuracy of duBois' formula to estimate the body surface area (*27*) is not verified in the Japanese population. Thus, we used the Cockcroft-Gault equation to estimate GFR without normalization by body surface area (mL/min/1.73 m^2) and adjusted for body size afterward using BMI. The second limitation involves the method of quantifying proteinuria. In this study, the presence of proteinuria was diagnosed by a positive protein screen as measured by a semiquantitative dipstick test for spot-urine, where a urinary protein level ≥30 mg/dL indicated a positive result. This approach did not allow us to distinguish subjects with microalbuminuria from those with overt proteinuria. Studies should be conducted to investigate the important issue of albuminuria.

In conclusion, the present study demonstrated that MHT, like SHT, is closely related to CKD, and HBP measurement could be a useful screening strategy to detect CKD in the general population. Whether suppression of CKD by therapeutic intervention in patients with MHT should be attempted must be clarified.

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Original Article

Fruit and Vegetable Consumption and the Risk of Hypertension Determined by Self Measurement of Blood Pressure at Home: The Ohasama Study

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It is well recognized that high fruit and vegetable consumption is associated with a reduction of blood pressure (BP) measured by conventional BP measurement in Western countries; however, there is little evidence about these associations in other regions and there have been no reports on these associations using self-measured BP at home (home BP). The objective of this work was to investigate the associations of fruit and vegetable consumption and their related micronutrients with the reduction of hypertension risk by using home BP in Japanese residents. Data were obtained from 1,569 residents aged 35 and over who measured their home BP in a general population of Ohasama, Japan. Dietary intake was measured using a 141-item food-frequency questionnaire (FFQ) and then subjects were divided into tertiles according to fruit, vegetable, potassium, vitamin C, and β-carotene consumption. Hypertension was defined as home systolic/diastolic BP≥135/85 mmHg and/or the use of antihypertensive medication. The prevalence of home hypertension was 39.4% for men and 29.3% for women. After adjustment for all potential confounding factors, the highest-tertile consumptions of fruits, vegetables, potassium, and vitamin C were associated with a significantly lower risk of hypertension (45%, 38%, 46%, and 43% lower risk of home hypertension, respectively). In conclusion, this cross-sectional study based on home BP measurement suggests that high-level consumptions of fruits, vegetables, potassium, and vitamin C are associated with a significantly lower risk of hypertension. (*Hypertens Res* 2008; 31: 1435–1443)

***Key Words*: fruit consumption, vegetable consumption, home blood pressure, hypertension, Japanese resident**

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Introduction

Hypertension is a major cause of morbidity and mortality (*1*). Many studies have indicated that high blood pressure (BP) is significantly associated with mortality (*2*) and increased risk of cardiovascular disease (CVD) events (*3*, *4*).

Numerous studies have reported that certain lifestyle choices, such as maintaining a normal body weight, engaging in routine physical activity, and reducing sodium and alcohol intake, can lead to undeniable reductions in BP levels and the prevalence of hypertension (*5*). Among these preventive factors, it is well acknowledged that dietary factors play an important role in the modulation of BP in hypertensive or normotensive individuals (*5–15*). Fruit and vegetable consumption has an especially powerful association with lower levels of BP and a lower risk of hypertension (*7*, *14*, *15*). Intake of potassium, calcium, magnesium, fiber, and protein derived from plants have also been shown to be associated with lower levels of BP (*7*, *8*, *15–17*).

However, most studies have focused mainly on community residents or high risk subjects in Western countries, and there have been few reports on the relationship of diet to BP in Asian populations. Since there are geographical differences in types of food consumption and risk factors among countries (*18*, *19*), it is important to confirm the reproducibility of previous results regarding the association between BP and food and nutrient components for individual populations.

Furthermore, most of these previous studies used conventional BP (CBP) measurements taken in medical settings. CBP measurement can lead to the white-coat effect which is a condition characterized by an elevated BP in a medical setting (*20*). Thus previous studies may have overestimated the risk of high BP. Self-measurement of BP at home is not influenced by observer or regression dilution biases or the white-coat effect (*20–24*). Furthermore, home BP measurements make it possible to obtain multiple measurements over a long observation period under relatively controlled conditions (*21*, *24*). Because of these benefits, home BP measurements are now widely used and recommended in several national and international guidelines (*25*, *26*). Home BP measurements are now considered more accurate and reliable to reflect target organ damage and the prognosis of cardiovascular disease than CBP measurement taken in a medical setting (*21–27*).

The aim of this study was to investigate the association of fruit and vegetable consumption with the risk of hypertension diagnosed by home BP.

Methods

Ohasama Study

The present study is a part of the Ohasama study, a longitudinal community-based observational study of individuals who have participated in the study of home BP measurement project in Ohasama, Iwate Prefecture, Japan. The geographic and demographic characteristics of study subjects have been reported previously (*23*, *28*).

This study was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government and informed consent was obtained from all subjects.

Subjects

The total population of Ohasama was 7,202 in 1998. Among this total, 4,964 were 35 years or over. Two-hundred thirteen subjects were excluded from the study because they were hospitalized, mentally ill, or bedridden, and 1,410 subjects who worked outside of the town were also excluded. Of the remaining 3,341 eligible subjects, 1,931 subjects (808 men and 1,123 women) gave their informed consent to participate in the study of home BP measurements. A total of 362 subjects (166 men and 196 women) were excluded for the following reasons: <3 measurements of home BP (n=114; 58 men and 56 women), incomplete questionnaire (n=167; 81 men and 86 women), or extreme levels of energy intake (above or below 2.5% of the range for all participants: n=81; 27 men and 54 women). Finally, data from 1,569 individuals (642 men and 927 women) were analyzed.

Variables

Home BP Measurement

Home BP was measured using the HEM701C (Omron Healthcare Co. Ltd., Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric method (*29*), which generates a digital display of both systolic BP (SBP) and diastolic BP (DBP). These devices have been previously validated (*29*) and satisfy the criteria of the Association for the Advancement of Medical Instrumentation. Since the arm circumference was usually <34 cm, we used a standard arm cuff (*30*).

Prior to measurement, physicians and public health nurses conducted health education classes to teach the participants how to measure their own BP. They also assessed whether the participants were able to measure their own BP correctly. Of the households in the town, 80% attended the classes, and public health nurses visited all of the remaining households to provide similar information (*28*, *31*). The participants were then asked to measure and record their BP once every morning for 4 weeks within 1 h of awakening, before breakfast and before taking any drugs, while seated and after an at least 2-min rest. The participants measured their BP at least twice on each occasion, although only the first value on each occasion was recorded on the worksheet to exclude selection bias by the participants (*24*). In the present study, home BP was defined as the mean of all first measurements recorded during the 4-week period. The mean (±SD) number of home BP measurements was 22±6. Hypertension was defined as use of antihypertensive medication and/or a home BP value of 135/

85 mmHg or over.

Food Frequency Questionnaire

Standardized methodology was used to calculate fruit and vegetable consumption and their related nutrients from data obtained in a Japanese version of the food-frequency questionnaire (FFQ). The reproducibility and validity of this questionnaire have been reported in detail (*32*). In brief, the studies were conducted to examine the validity of 17 specific nutrients of interest (*32*). The participants in the present study were similar and lived in northeast Japan. Pearson's correlation coefficient was used to compare nutrients recorded in the four 3-d diet records over a 1-year period with those in two FFQs obtained with a 1-year interval between them to take into account seasonal variations in food consumption. Seventeen nutrients were analyzed and the correlations ranged from 0.24 to 0.85 (median 0.43) for the first FFQ, and from 0.47 to 0.91 (median 0.68) for the second. The observed r^2 value between every nutrient and the 141 selected food items from the FFQ data was >0.9. We examined the consumption of 14 fruits and 19 vegetables. The questionnaire asked about the average frequency of consumption of each food during the previous year. The nine frequency categories ranged from no consumption to seven or more times per day. A standard portion size of one serving was specified for each food, and respondents were asked if their usual portion was larger (>1.5 times), the same, or smaller (<0.5) than the standard. In the present study, we took into account energy from alcohol from foods, *e.g.*, certain seasonings that include alcohol. But we did not consider alcohol derived directly from beer, wine, or other alcoholic beverages, in the total energy count. Nutritional supplements were not taken into account because there were few supplement users. In order to determine the efficacy of the nutrients of the food groups studied, the dietary contents of nutrients, *i.e.*, potassium, vitamin C and β-carotene, were estimated by analyzing the FFQ results. All food consumption and nutrients were adjusted for total energy intake using the residual method (*33–35*). Following this procedure, subjects were divided into tertiles to indicate low, medium, and high levels of each food and nutrient consumption.

Other Putative Confounding Factors Related to BP

With regard to smoking habits, subjects were defined as nonsmokers, which included never- and ex-smokers, or current smokers. Alcohol consumption was defined as rarely or never; <540 mL of sake/d; or ≥540 mL of sake/d (540 mL of sake=81 g of alcohol). With regard to frequency of exercise, subjects were also categorized according to their answer to the question, "How many times do you normally exercise per week?" The responses were divided into three groups according to the frequency of exercise: rarely or never (<1 h/week); 1 or 2 h/week; and ≥3 h/week. Anthropometric measures (height, body weight) were recorded by a standardized protocol. The body mass index (BMI) was calculated as weight (kg)/height^2 (m^2) and was classified as under- or normal weight (≤24.9 kg/m^2), and overweight (≥25.0 kg/m^2). Trained public health nurses measured anthropomorphic parameters at the time of the annual health check. Past history of diabetes and hypercholesterolemia was also taken into account in the study.

Table 1. Characteristics of All Subjects (n=1,931)

Factors	Non participants	Participants	p-value
No. of subjects	362	1,569	
Gender (men, %)	45.6	41.0	0.062
Age	63.4±14.4	60.0±12.8	<0.0001
Alcohol consumption (%)			0.357
Rarely or never	57.2	61.3	
<540 mL/d	38.2	34.8	
≥540 mL/d	4.5	3.9	
Smoking status (%)			0.002
Never	69.6	71.7	
Ex-smoker	12.7	7.3	
Current	17.7	21.0	
Frequency of exercise (%)			0.918
Rarely or never	6.4	6.0	
1 or 2 h/week	13.3	14.0	
≥3 h/week	80.4	80.1	
Energy and nutrients			
Total energy (kcal/d)	2,607±1,929	2,442±940	0.018
Fat (g/d)*	67.4±17.6	62.3±13.8	<0.0001
Sodium (mg/d)*	6,929±3,132	6,319±1,899	<0.0001
BMI (≥25 kg/m^2, %)	7.7	14.4	<0.0001
Home BP (mmHg)			
Systolic	128±12	122±15	<0.0001
Diastolic	77±10	75±9	0.004

*Data were adjusted for total energy by the residual method. Continuous variables are presented as mean±SD. BMI, body mass index.

Statistical Analysis

The data of all subjects are expressed as the mean±SD or percentages. Differences between social and lifestyle characteristics of each fruit and vegetable intake were tested for statistical significance with Student's t-test, analysis of variance (ANOVA) for continuous variables or χ^2 test for categorical variables. To examine how the consumption of fruits and vegetables or other related nutrients was associated with a risk of hypertension (defined on the basis of home BP measurement), we conducted multiple logistic regression analyses after adjustment for the following putative confounding factors: sex, age, BMI, frequency of exercise, smoking status, alcohol consumption, energy-adjusted fat intake and sodium consumption, and past history of diabetes and hypercholester-

Table 2. Distribution of Characteristics across Tertile of Fruit and Vegetable Consumption (n=1,569)

Factors	Fruit				Vegetable			
	Lowest (n=523)	Medium (n=523)	Highest (n=523)	p-value	Lowest (n=523)	Medium (n=523)	Highest (n=523)	p-value
Mean consumption (g/d)	15.6	84.2	222.7		18.5	56.8	112.7	
Gender (men, %)	62.3	38.6	21.8	<0.0001	67.3	34.8	20.7	<0.0001
Age	57.8±13.1	61.2±13.0	61.0±11.9	<0.0001	57.2±13.1	61.3±13.1	61.5±11.6	<0.0001
Alcohol consumption (%)				<0.0001				<0.0001
Rarely or never	40.3	61.8	70.0		41.5	62.5	68.1	
<540 mL/d	51.2	35.0	28.1		50.1	34.6	29.6	
≥540 mL/d	8.4	3.3	1.9		8.4	2.9	2.3	
Smoking status (%)				<0.0001				<0.0001
Never	57.6	73.4	84.5		54.3	75.1	86.0	
Ex-smoker	9.4	7.8	4.2		10.9	6.3	4.2	
Current	33.1	18.7	11.3		34.8	18.5	9.8	
Frequency of exercise (%)				0.187				0.758
Rarely or never	6.1	5.9	5.7		5.4	6.3	6.1	
1 or 2 h/week	17.0	12.8	12.2		15.3	12.0	14.7	
≥3 h/week	76.9	81.3	82.0		79.3	81.6	79.2	
Energy and nutrients								
Total energy (kcal/d)	2,609±812	1,894±783	2,371±831	<0.0001	2,584±804	1,926±797	2,364±849	<0.0001
Fat (g/d)*	58.9±16.2	61.6±11.1	61.5±11.6	0.001	55.7±15.0	62.3±10.4	64.0±12.4	<0.0001
Sodium (mg/d)*	5,813±2,205	6,296±1,651	6,765±1,814	<0.0001	5,090±1,740	6,196±1,252	7,888±1,897	<0.0001
BMI (≥25 kg/m^2, %)	11.3	16.1	15.9	0.045	10.3	14.3	18.5	0.001
Prevalence of hypertension (%)	35.2	35.6	29.6	0.075	33.3	31.4	35.8	0.319
Using antihypertensive medication (%)	17.6	19.1	19.1	0.764	14.1	18.9	22.8	0.002
Home BP in untreated participants (mmHg)								
Systolic	121±12	120±16	117±14	<0.0001	121±13	119±14	118±14	0.001
Diastolic	76±9	74±10	73±9	<0.0001	76±9	73±9	73±9	<0.0001

*Data were adjusted for total energy by the residual method. Continuous variables are presented as mean±SD. Analysis of variance (ANOVA) for continuous variables or χ^2 test for categorical variables were used for the comparison across tertiles of consumption of fruit and vegetables. BMI, body mass index; BP, blood pressure.

olemia. We tested the interaction among these factors by introducing a multiplicative term into the models.

For all analyses, statistical significance was defined as a two-tailed p value <0.05. All analyses were conducted using SPSS software version 12 for Windows (SPSS Inc., Chicago, USA).

Results

The mean consumptions of fruits and vegetables were 108 and 63 g/d, respectively. The mean home SBP/DBP levels were 122/75 mmHg. The mean BMI was 23.2±3.1 kg/m^2 for men and 23.4±3.1 kg/m^2 for women. Percentages of past history of diabetes and hypercholesterolemia were 9.8% and 2.6% for men and 9.0% and 5.5% for women, respectively. Percentages of subjects receiving antihypertension medication were 18.4% for men and 18.8% for women. The prevalences of home hypertension, which was defined as the use of antihypertensive medication and/or a home BP value of 135/85 mmHg or over, were 39.4% for men and 29.3% for women.

Table 1 compares the characteristics of the included study subjects with those who participated in the study but who were ultimately excluded based on the exclusion criteria. Those who completely fulfilled the study criteria were characterized by a higher proportion of current smokers, a lower amount of total energy intake, and a higher BMI.

Table 2 shows the relationships of social and lifestyle characteristics of potential risk factors for hypertension in each category of fruit and vegetable consumption. Compared with those in the lowest tertile of fruit consumption, those in the highest-tertile were more likely to be women, never or ex-smokers, and older. They were also likely to have higher BMI and lower amounts of alcohol consumption. We observed similar tendencies for vegetable consumption. The frequency of exercise did not differ among the fruit and vegetable con-

Table 3. Odds Ratio (95% Confidence Interval) for the Association between Fruit and Vegetable Consumption and the Risk of Home Hypertension (n=1,569)

	No.	Adjusted*	p-value	Adjusted#	p-value
Fruit					
Highest	523	0.65 (0.47–0.91)	0.011	0.55 (0.37–0.81)	0.002
Medium	523	0.86 (0.63–1.17)	0.324	0.82 (0.57–1.18)	0.291
Lowest	523	Ref.		Ref.	
p for trend		0.038		0.009	
Vegetable					
Highest	523	0.84 (0.60–1.17)	0.306	0.62 (0.40–0.95)	0.029
Medium	523	0.69 (0.50–0.95)	0.023	0.57 (0.39–0.84)	0.005
Lowest	523	Ref.		Ref.	
p for trend		0.076		0.012	
Potassium					
Highest	523	0.70 (0.50–0.99)	0.045	0.54 (0.32–0.88)	0.015
Medium	522	0.69 (0.49–0.96)	0.028	0.48 (0.31–0.73)	0.001
Lowest	524	Ref.		Ref.	
p for trend		0.057		0.003	
Vitamin C					
Highest	522	0.75 (0.54–1.05)	0.089	0.57 (0.37–0.87)	0.010
Medium	524	0.83 (0.60–1.15)	0.258	0.70 (0.48–1.02)	0.064
Lowest	523	Ref.		Ref.	
p for trend		0.226		0.030	
β-Carotene					
Highest	522	0.75 (0.53–1.07)	0.113	0.67 (0.42–1.06)	0.087
Medium	523	0.81 (0.58–1.12)	0.200	0.69 (0.46–1.03)	0.067
Lowest	524	Ref.		Ref.	
p for trend		0.253		0.136	

*Adjusted for age, gender, and BMI. #Adjusted for age, gender, BMI, frequency of exercise, smoking status, alcohol consumption, fat intake, sodium consumption, and past history of diabetes and hypercholesterolemia. BMI, body mass index.

sumption tertiles. Although the highest vegetable consumption tertile was significantly related to higher prevalence of using antihypertensive medication and the lower fruit and vegetable consumption tertiles were associated with higher home BP in untreated participants, the prevalence of hypertension was not related to the consumption levels.

Table 3 shows the association between fruit and vegetable consumption and the reduction of home hypertension risk in the total subjects. Since we had confirmed that the association was similarly observed in men and women (data not shown), we combined both sexes in the analysis. In the sex- and BMI-adjusted analysis, the highest-tertile of fruit consumption showed a significant relationship with a lower risk for home hypertension (the highest-tertile for fruit consumption: odds ratio 0.65, p=0.011). After adjustment for known risk factors for hypertension such as age, gender, BMI, frequency of exercise, smoking status, alcohol consumption, fat intake, sodium consumption, and past history of diabetes and hypercholesterolemia, these associations did not change. Compared to the lowest fruit consumption tertile, a 45% lower risk of home hypertension was found in those in the highest fruit consumption tertile (p=0.002). The highest vegetable consumption tertile the highest consumption tertile for other related nutrients also showed significant positive associations with lower risks of home hypertension (the highest-tertile for vegetable consumption: 0.62, p=0.029; the highest-tertile for potassium: 0.54, p=0.015; and the highest-tertile for vitamin C: 0.57, p=0.010). In this study, no significant interaction was found between the consumption of fruits, vegetables or the other related nutrients and putative confounding factors. The results did not change when adjusted for absolute sodium intake instead of "total energy-adjusted" (residual method) sodium intake (data not shown).

Discussion

The foregoing analysis demonstrated that high level consumptions of fruits, vegetables, and other related micronutrients, *i.e.*, potassium and vitamin C, are potentially associated with a lower risk of uncontrolled hypertension. The association did not alter after adjustment for putative confounding factors.

Fruit/Vegetable Consumption and Home Hypertension

We found that high-level consumptions of fruits and vegetables were associated with a significantly lower risk of hypertension as measured by home BP. The results from several previous studies examining the association between fruit and vegetable consumption and CBP using a combination of fruits and vegetables are partially consistent with the present findings (*7*, *14*, *15*). The Seguimiento Universidad de Navarra study demonstrated that high-level consumption of vegetables was inversely associated with BP levels, whereas they did not find any associations with fruit consumption (*36*). Geographical differences in types of food consumption might be related to BP levels. In the present study, we also found a significant association between the medium-level consumption of vegetables and a lower risk of hypertension. The present study showed that those who consumed more fruits and vegetables also had higher fat and sodium intake. This might have been attributable to cooking methods, such as the use of soy sauce, table salt, and other seasonings, or the method of cooking vegetables, such as deep frying. The higher fat intake among those who consumed more fruit might have been attributable to the close correlation between the consumption of fruits and vegetables and the consumption of fats.

Other Related Micronutrients and Home Hypertension

In the present study, we found strongly significant associations between high potassium and vitamin C intake and a lower risk of home hypertension. Several mechanisms have been proposed to explain the inverse association between these nutrients and BP or risk of hypertension, including the idea that the antioxidant properties of these nutrients reduce BP. The observation of an inverse relationship between potassium intake and BP was consistent with previous studies (*37*, *38*). We also found a tendency for β-carotene to reduce the risk of hypertension, although this effect was not statistically significant. However, such an effect of β-carotene is still considered controversial. Several epidemiological studies have suggested an inverse association between dietary intake of fruits and vegetables containing β-carotene and BP levels and a risk of developing hypertension (*39*, *40*), but in randomized control trials using β-carotene supplements, these associations were inconsistent (*41–43*). Since intervention trials using vitamin supplements in an attempt to reduce mortality from cardiovascular disease have produced little evidence (*7*, *44*), or sometimes suggested harmful effects (*45*), current evidence points to the beneficial effects of eating more fruits and vegetables containing β-carotene rather than supplementation. Further prospective studies would be useful to specifically clarify how dietary micronutrients are related to the progression of hypertension and to risk factors for hypertension.

It is generally known that intake of vitamin C has a strong correlation with high-level fruit and vegetable consumption. Thus, a high vitamin C intake seems to contribute to lower BP levels. The effect of vitamin C on BP is also still disputable. A previous study indicated that the total vitamin C intake (food plus supplements) seems to be less associated with lower BP than the intake of fruits and vegetables themselves (*46*). Another study also reported that there were no beneficial effects from low-dose antioxidant supplementation that included vitamin C and vitamin E in a 6.5-year randomized analysis of BP (*41*). It seems that increased intake of a certain nutrient alone might not fully contribute to lowering BP. A combination of vitamins and minerals may be needed in order to prevent BP elevation.

On the other hand, there is evidence that some antihypertensive medications, such as angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, increase the risk of hyperkalemia (*47–49*), so dietary education or advice by doctors, pharmacists, or dieticians may often include the admonition to avoid foods containing high levels of potassium, such as bananas and prunes. For this reason, subjects who were using antihypertensive medication may have tended to avoid eating foods containing high levels of potassium.

Study Strengths and Limitations

Home BP can eliminate several biases, including the white-coat effect (*20–23*, *28*), and thus a strength of the present study was that the results may have more accurately assessed the relationship between BP and fruit/vegetable consumption than similar studies using office BP. Thus, we could say that those who did not use antihypertensive medication but had uncontrolled home hypertension were a high risk group, and accurate early diagnosis or highly consciousness of high BP and subsequent medication or dietary intervention are expected to clarify in general subjects.

Several limitations of the present study need to be discussed. First, we could not determine whether additional sodium was consumed in the form of table salt or salt added during cooking. Also, we did not monitor the consumption of pre-packaged, convenience, or fast-foods, or the frequency of high-sodium restaurant foods. Even though we found that sodium intake in our FFQ was correlated with sodium intake in the four 3-d diet records over a 1-year period, neither method is very reliable for assessing dietary salt intake in particular, because they do not estimate the discretionary salt intake. Therefore, the true sodium intake might be underestimated.

Second, the information on food and nutrient consumption in the present study were obtained on the basis of a dietary recall. The correlation between the FFQ and the actual diet has been well established, but several problems remain. For example, the FFQ has a limited number of items and minimal information about portion size and it is not intended to provide accurate estimates of absolute intake. On the other hand, dietary assessment of sodium is considered to be difficult

because of the wider "intra-subject" variation (*50*), and the difficulty in the assessment of seasoning. Although the measurement of urinary sodium excretion using urine samples collected over multiple days might be considered a reliable method, it would be very hard in general to estimate sodium intake by dietary survey (*51*, *52*). Lastly, since the present study was cross-sectional, further follow-up is required to clarify the relationship between fruit and vegetable consumption and the risk of developing hypertension.

Furthermore, the possibility of selection bias needs to be considered when generalizing the present findings, because only 47.0% of those eligible to participate in the study agreed to take part and the nonparticipants were older, and had higher BP levels and higher energy intake in comparison to those who participated in the study: it is possible that the participants had to be sufficiently independent to participate in this survey based on self-reported FFQ. Moreover, marked differences also exist in the epidemiology of home hypertension between Japan and the Western countries (*53*). Thus further research in other ethnic and cultural populations is needed to confirm the generalizability of our findings.

In the present study, we found an association between low-level consumption of fruits and increased risk of uncontrolled hypertension among subjects who did not use antihypertensive medication. However, since all subjects who were receiving antihypertensive medication had been diagnosed with hypertension, their dietary habits may already have been changed.

The risk of hypertension could be attributable to other food groups. For example, Kihara *et al.* reported that inorganic sulfate/urea nitrogen, an index related to the dietary score of sulfur-containing amino acids derived mainly from animal protein, were both negatively associated with SBP (*37*). However, even though other studies have reported that consumption of high levels of fruits and vegetables could be independently associated with a lower risk of hypertension, such evidence is less frequently reported in Asian populations. Furthermore, since people consume diets consisting of a variety of foods with complex nutrient combinations, focusing on only single nutrients or foods could result in the identification of erroneous associations between dietary factors and disease. A dietary pattern approach using factor and cluster analyses could provide more useful information about the risks of home hypertension in future studies.

Conclusions

The present results from the Ohasama study suggest that high-level consumptions of fruits, vegetables, and other related micronutrients present mainly in fruits and vegetables are potentially associated with a lower risk of hypertension. While the mechanism for BP-lowering *via* fruit and vegetable consumption is not yet clear (*54*, *55*), selective consumption of healthy foods and nutrients may lead to prevention and treatment of hypertension.

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Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort: The Suita Study

Yoshihiro Kokubo, Kei Kamide, Tomonori Okamura, Makoto Watanabe, Aya Higashiyama, Katsuyuki Kawanishi, Akira Okayama and Yuhei Kawano

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Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort

The Suita Study

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Abstract—Few prospective studies have examined the association between high-normal blood pressure and cardiovascular disease (CVD) in Asia. We examined the impact of high-normal blood pressure on the incidence of CVD in a general urban population cohort in Japan. We studied 5494 Japanese individuals (ages 30 to 79 years without CVD at baseline) after completing a baseline survey who received follow-up through December 2005. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, we documented the incidence of 346 CVD events. The frequencies of high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 18.0%, 20.1%, and 10.1% for men and 15.9%, 15.6%, and 8.8% for women, respectively. Antihypertensive drug users were also classified into the baseline blood pressure categories. Compared with the optimal blood pressure group, the multivariable hazard ratios (95% confidence intervals) of CVD for normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) in men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) in women, respectively. The risks of myocardial infarction and stroke for each blood pressure category were similar to those of CVD. Population-attributable fractions of high-normal blood pressure and hypertension for CVD were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively. In conclusion, high-normal blood pressure is a risk factor for the incidence of stroke and myocardial infarction in a general urban population of Japanese men. **(*Hypertension*. 2008; 52:652-659.)**

Key Words: cardiovascular diseases ■ epidemiology ■ general population ■ high-normal blood pressure ■ myocardial infarction ■ prospective studies ■ stroke

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD)[1–5] in both developing and developed countries.[2,6,7] The guidelines of the Joint National Committee 7 from the United States has recently introduced a category, designated "prehypertension," for people with blood pressures ranging from 120 to 139 mm Hg for systolic pressure or 80 to 89 mm Hg for diastolic pressure.[8] The European Guidelines[9] and Japanese Society of Hypertension Guidelines,[10] however, divide this population into 2 groups: those with systolic blood pressures between 120 and 129 mm Hg or diastolic blood pressures between 80 and 84 mm Hg are classified as normal, whereas those with systolic blood pressures between 130 and 139 mm Hg or diastolic blood pressures between 85 and 89 mm Hg are classified as high-normal. Although the association of cardiovascular risk with elevated blood pressure is well accepted,[1–4,6] only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. The Framingham Heart Study revealed an association of high-normal blood pressure with increased risk of CVD.[11] The Framingham coronary heart disease prediction functions perform well for whites and blacks in different settings; these findings can be applied to other ethnic groups, like in the ARIC study, after recalibration for differing prevalence of risk factors for coronary heart disease events.[12] Few studies have investigated the association between blood pressure category and the incidence of CVD in Japan,[5,13] where there is a higher incidence of stroke and lower incidence of myocardial infarction (MI) than those in Western countries.[7] We performed a prospective examination of the risk of stroke and MI in men and women according to blood pressure category comparing normal and high-normal blood pressures in a general urban Japanese population.

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Methods

Study Subjects

The Suita Study,[5,14,15] an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 12 200 Japanese residents of Suita. As a baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n=208), were missing data (n=170), attended health checkups after April 1994 (n=79), or failed to complete the follow-up health surveys or questionnaires after baseline examination (n=534). After applying these exclusions, 5494 individuals were included in the analysis.

Measurement of Blood Pressure and Covariates

Well-trained physicians measured blood pressure 3 times in a seated position with a mercury column sphygmomanometer and an appropriately sized cuff according to standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic blood pressure was measured first to obtain approximate systolic blood pressure levels. Systolic (SBP) and diastolic (DBP) blood pressures were the average of the second and third measurements recorded more than 1 minute apart.

At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal blood pressure (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), hypertension Stage 1 (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg), or hypertension Stage ≥2 (SBP ≥160 mm Hg or DBP ≥100 mm Hg).[9,10] Antihypertensive drug users were classified according to their blood pressure levels at baseline survey. Due to the small sample size for Grade 3 hypertension, both Grades 2 and 3 were combined. Therefore, we compared optimal blood pressure with Grade 1 and Grades 2 plus 3 hypertension in this study. In addition, after antihypertensive drug users were classified into the hypertension Stage ≥1 group, subjects were classified into one of the 4 blood pressure categories: optimal, normal, and high-normal blood pressure and hypertension Stage ≥1 group. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the 2 blood pressure categories.

At the baseline examination, we performed routine blood tests, including serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose levels. Physicians or nurses administered questionnaires regarding individual personal habits and present illnesses. Subjects were classified as current smokers, nonsmokers, and past smokers. We also measured height and body weight in a fasting state. Body mass index was calculated as weight (kg) divided by the square of the height (m^2). Hyperlipidemia was defined as total serum cholesterol levels ≥5.7 mmol/L (220 mg/dL) and/or current use of antihyperlipidemic medications. Diabetes was defined as fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) and/or current use of antidiabetic medications. We obtained informed consent from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Confirmation of Strokes and Myocardial Infarctions

Five hospitals in the Suita area were capable of performing CT scans and/or MRI, all of which were the major hospitals to which patients with acute stroke and those with MI were admitted. Medical records were reviewed by registered hospital or research physicians who were blinded to the baseline data. Stroke and MI events were registered if they occurred between the date on which the baseline health examination was performed and December 31, 2005. Strokes were defined according to the US National Survey of Stroke criteria,[16] which require rapid onset neurological deficits lasting at least 24 hours or until death. For each stroke subtype (cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definitive diagnosis was established based on CT, MRI or autopsy. Definitive and probable MIs were defined according to the criteria set by the MONICA project,[17] which requires electrocardiographic evidence, cardiac enzyme elevations, and/or autopsy. Sudden death was defined as death of unknown origin occurred within 24 hours from onset.

To complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates without registration of CVD incidence, which were defined as probable stroke or MI. CVD was defined as stroke and MI in this study.

End Point Determination

The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored). To detect MI and stroke occurrences, each participant's health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. We also obtained informed consent to review in-hospital medical records for 86.2% participants who were suspected to have signs or symptoms related to stroke or MI events.

Statistical Analysis

Analysis of variance and χ^2 tests were used to compare the mean values and frequencies by sex according to blood pressure category. For each subject, person-years of follow-up were calculated from the date of baseline survey, to the first end point, CVD event, death, emigration, or December 31, 2005. The Cox proportional hazard ratios (HRs) were fit for each blood pressure category after adjusting for age and other potential confounding factors, including age, present illness of hypercholesterolemia or diabetes, smoking status (nonsmoker, past smoker, and current smoker), and drinking status (nondrinker, past drinker, and current drinker) at baseline survey.

To express the impact of blood pressure categories on CVD occurrence in the participants, we estimated the population-attributable fraction (%). Population-attributable fraction was estimated as $Pe \times (HR-1)/HR$, in which Pe is the proportion of incident cases in the blood pressure category and HR is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using SAS statistical package software (release version 8.2; SAS Institute Inc, Cary, NC).

Results

At baseline, we observed several differences in the distribution of CVD risk factors according to blood pressure categories (Table 1). The percentages of subjects with optimal, normal, and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively. On average, both men and women with higher blood pressure were older and had higher serum total cholesterol levels, higher body mass index, and higher incidences of hyperlipidemia and diabetes than those with optimal blood pressure. The percentages of antihypertensive drug users classified as having hypertension Stages 1 and ≥2 at baseline were 21.3% and 37.7% for men and 24.2% and 40.6% for women, respectively.

Table 1. Baseline Characteristics of Study Subjects According to Blood Pressure Category

Groups and Variables	Blood Pressure Category*					*P* Values
	Optimal	Normal	High-Normal	Stage 1	Stage ≥2	
Men						
No. of subjects	803	502	463	516	286	
Age, years	50.8±13.2	54.0±12.9	57.5±12.2	60.1±11.7	62.0±11.1	<0.001
SBP, mm Hg	107.8±7.5	121.7±5.4	131.4±5.8	143.9±8.5	167.0±17.4	<0.001
DBP, mm Hg	68.2±6.7	76.6±6.3	81.2±6.9	87.5±8.2	97.0±11.7	<0.001
Total cholesterol, mmol/L†	5.1±0.8	5.2±0.9	5.3±0.9	5.3±0.9	5.3±0.9	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.3±0.3	1.3±0.4	1.3±0.3	1.3±0.3	1.3±0.3	0.332
Body mass index, kg/m^2	22.0±2.7	22.7±2.6	23.2±2.7	23.3±3.0	23.6±3.2	<0.001
Antihypertensive medication, %	0.6	3.9	7.7	21.3	37.7	<0.001
Hyperlipidemia, %	23.7	27.4	30.6	34.4	31.4	<0.001
Diabetes, %	3.8	5.3	5.6	8.9	9.7	<0.001
Current smokers, %	59.7	49.6	46.3	44.3	40.9	<0.001
Current drinkers, %	71.7	77.0	75.0	76.8	79.6	0.045
Women						
No. of subjects	1240	504	465	457	258	
Age, years	47.8±11.9	54.0±11.5	58.9±11.5	61.6±9.4	62.9±9.6	<0.001
SBP, mm Hg	105.5±7.9	122.4±4.8	132.4±4.9	145.7±7.8	169.9±14.0	<0.001
DBP, mm Hg	66.4±6.6	75.5±7.1	79.7±6.9	85.0±9.0	92.3±13.9	<0.001
Total cholesterol, mmol/L†	5.2±0.9	5.6±1.0	5.7±0.9	5.9±0.9	5.8±1.0	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.5±0.3	1.4±0.3	1.4±0.3	1.4±0.3	1.4±0.3	<0.001
Body mass index, kg/m^2	21.1±2.7	22.5±3.0	22.8±3.2	23.2±3.3	23.7±3.7	<0.001
Antihypertensive medication, %	0.9	4.3	11.3	24.2	40.6	<0.001
Hyperlipidemia, %	28.8	44.2	50.9	58.6	58.1	<0.001
Diabetes, %	1.5	3.3	4.0	6.7	5.8	<0.001
Current smokers, %	15.6	11.7	9.2	6.9	8.9	<0.001
Current drinkers, %	37.0	32.5	27.9	29.8	25.4	<0.001

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Plus–minus values are means±SD.

†To convert cholesterol values to mg/dL, multiply ×38.67.

During an average 11.7-year follow-up period, we documented 213 strokes (155 definitive strokes and 58 probable strokes) consisting of 141 cerebral infarctions, 32 intracerebral hemorrhages, 22 subarachnoid hemorrhages, and 18 unclassified strokes. We also documented 133 MIs (64 definitive MIs and 69 probable MIs or sudden cardiac deaths). Subjects who moved from Suita (16.8% of the total participants) were censored at that time.

We determined the age- and multivariable-adjusted hazard ratios for CVD, MI, and stroke according to blood pressure categories in the presence or absence of antihypertensive medication (Table 2). In men, the multivariable HRs (95% CIs) of CVD incidence were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) for men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) for women with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively. The risks of MI and stroke for each blood pressure category were similar to the risk of CVD. In a combined analysis of men and women, the multivariable HR of CVD incidence were 1.62 (1.08 to 2.43), 2.08 (1.42 to 3.05), 2.06 (1.42 to 2.98), and 3.53 (2.43 to 5.13) for the normal and high-normal blood pressure and hypertension Stages 1 and ≥2 groups, respectively (data not shown). In addition, the multivariable HR of CVD incidence in men and women younger than 60 years old were similar to those seen in men and women older than 60 years of age (data not shown).

In a second analysis in which all antihypertensive drug users were categorized to the Stage ≥1 group, we determined the age- and multivariable-adjusted HRs for CVD, MI, and stroke according to blood pressure category (Table 3). In men, the multivariable HRs (95% CIs) of CVD incidence were 1.83 (1.05 to 3.20), 2.11 (1.22 to 3.64), and 3.20 (2.01

Table 2. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category With and Without Antihypertensive Medications

Groups and Variables	Blood Pressure Category*				
	Optimal	Normal	High-Normal	Stage 1	Stage ≥2
Men					
Person-years	9724	5889	5127	5611	3025
Cardiovascular disease					
Case	23	34	43	57	52
Age-adjusted	1	2.03 (1.19–3.46)	2.42 (1.45–4.03)	2.44 (1.49–3.99)	3.71 (2.25–6.16)
Multivariable-adjusted	1	2.04 (1.19–3.48)	2.46 (1.46–4.14)	2.62 (1.59–4.32)	3.95 (2.37–6.58)
MI					
Case	10	14	19	25	20
Age-adjusted	1	2.07 (0.92–4.68)	2.56 (1.18–5.53)	2.45 (1.16–5.17)	3.47 (1.60–7.51)
Multivariable-adjusted	1	2.14 (0.94–4.86)	2.65 (1.20–5.85)	2.72 (1.26–5.84)	3.89 (1.76–8.56)
Stroke					
Case	13	20	24	32	32
Age-adjusted	1	2.13 (1.06–4.30)	2.39 (1.21–4.71)	2.49 (1.30–4.78)	4.17 (2.17–8.01)
Multivariable-adjusted	1	2.12 (1.04–4.30)	2.43 (1.21–4.86)	2.62 (1.35–5.09)	4.38 (2.24–8.56)
Women					
Person-years	15 438	6100	5391	5272	2812
Cardiovascular disease					
Case	25	17	28	29	38
Age-adjusted	1	1.05 (0.56–1.95)	1.48 (0.85–2.59)	1.32 (0.75–2.30)	3.00 (1.77–5.09)
Multivariable-adjusted	1	1.12 (0.59–2.13)	1.54 (0.85–2.78)	1.35 (0.75–2.43)	2.86 (1.60–5.12)
MI					
Case	7	5	10	9	14
Age-adjusted	1	1.09 (0.34–3.48)	1.71 (0.63–4.59)	1.38 (0.50–3.80)	3.56 (1.39–9.08)
Multivariable-adjusted	1	1.44 (0.42–4.90)	2.27 (0.78–6.57)	1.69 (0.56–5.10)	5.24 (1.85–14.85)
Stroke					
Case	18	12	18	20	24
Age-adjusted	1	1.05 (0.50–2.19)	1.39 (0.71–2.75)	1.29 (0.66–2.52)	2.83 (1.49–5.39)
Multivariable-adjusted	1	1.05 (0.49–2.24)	1.29 (0.63–2.67)	1.21 (0.61–2.45)	2.20 (1.07–4.50)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified according to their blood pressure levels at baseline survey.

to 5.09) for normal and high-normal blood pressure subjects without antihypertensive medication and subjects with hypertension Stage ≥1 with or without antihypertensive medication, respectively. In women, the multivariable HR of CVD incidence was 2.13 (1.25 to 3.62) for the hypertension Stage ≥1 group with or without antihypertensive medications. The risks of MI and stroke for high-normal blood pressure and hypertension Stage ≥1 group were observed in men (HR=2.32, 95% CI: 1.02 to 5.27 and HR=3.35, 95% CI: 1.64 to 6.80 for MI; HR=2.04, 95% CI: 1.00 to 4.22 and HR=3.33, 95% CI: 1.80 to 6.15 for stroke, respectively). HRs for CVD according to prehypertensive category excluding subjects taking antihypertensive drugs (Table 3) were similar but slightly lower than that category including subjects taking antihypertensive drugs (Table 2).

Using the HRs, we estimated the positive fraction of CVD attributable to exposure for each blood pressure category at baseline by sex (Figure). For men, 8.3%, 12.2%, 16.8%, and 18.5% of CVD incidence were excessive incidence due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2 with values of 1.3%, 7.1%, 5.4%, and 18.0%.

Discussion

In this cohort study of a general Japanese urban population, we determined that high-normal blood pressure was a risk factor for the incidence of stroke and MI in men in comparison to subjects with optimal blood pressure. In this study, 20.5% and 8.4% of CVD incidence may derive from prehypertension cases in men and women, respectively. This is the

Table 3. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category

	Blood Pressure Category*			
Groups and Variables	Optimal	Normal	High-Normal	Stage ≥1
Men				
Person-years	9670	5662	4805	9243
Cardiovascular disease				
Case	23	28	35	123
Age-adjusted	1	1.80 (1.03–3.13)	2.09 (1.23–3.55)	3.00 (1.91–4.72)
Multivariable-adjusted	1	1.83 (1.05–3.20)	2.11 (1.22–3.64)	3.20 (2.01–5.09)
MI				
Case	10	11	16	51
Age-adjusted	1	1.71 (0.72–4.03)	2.27 (1.02–5.03)	2.98 (1.49–5.93)
Multivariable-adjusted	1	1.78 (0.75–4.22)	2.32 (1.02–5.27)	3.35 (1.64–6.80)
Stroke				
Case	13	17	19	72
Age-adjusted	1	1.93 (0.93–3.98)	2.01 (1.00–4.08)	3.18 (1.75–5.79)
Multivariable-adjusted	1	1.92 (0.92–3.97)	2.04 (1.00–4.22)	3.33 (1.80–6.15)
Women				
Person-years	15 293	5890	4834	9002
Cardiovascular disease				
Case	24	12	20	81
Age-adjusted	1	0.80 (0.39–1.61)	1.28 (0.69–2.36)	2.12 (1.30–3.44)
Multivariable-adjusted	1	0.86 (0.42–1.72)	1.32 (0.69–2.53)	2.13 (1.25–3.62)
MI				
Case	7	4	7	27
Age-adjusted	1	0.91 (0.26–3.14)	1.38 (0.47–4.01)	2.23 (0.94–5.28)
Multivariable-adjusted	1	1.17 (0.31–4.34)	1.83 (0.58–5.75)	2.97 (1.11–7.91)
Stroke				
Case	17	8	13	54
Age-adjusted	1	0.76 (0.32–1.79)	1.22 (0.58–2.58)	2.12 (1.17–3.83)
Multivariable-adjusted	1	0.77 (0.32–1.83)	1.11 (0.50–2.49)	1.89 (1.00–3.58)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified into the hypertension Stage ≥1 group.

first cohort study to examine the impact of high-normal blood pressure on the risks of stroke and MI incidence in a general Japanese urban population, who have a relatively higher incidence of stroke and lower incidence of MI than those seen in Western countries.[7]

Compared with the previous studies, this study has several methodological strengths. First, we evaluated a large prospective cohort of people selected randomly from a general population in Japan, which allowed us to perform subanalyses by age and CVD subtype. Second, our cohort population was selected from an urban population in contrast to the majority of other cohorts in Japan, which have been selected from rural populations. Because approximately 66% of the Japanese population lives in urban areas, this is an important strength of our analysis. The health status of each participant was examined every 2 years during a clinical visit at the National Cardiovascular Center. In addition, a health questionnaire was administered to each participant yearly by mail or telephone. In combination with frequent evaluation of the CVD registry, we could effectively examine the incidence of CVD events in this population. Finally, we examined the risk of CVD incidence, which is a more direct measure of CVD risk than risk of CVD mortality, because mortality from CVD is significantly influenced by treatment.

This study revealed that normal and high-normal blood pressures were risk factors for CVD in Japanese urban men. The results of a multiple ethnic groups investigation has demonstrated that high-normal blood pressure is a risk factor for incidence of coronary heart disease in both men and women.[11] Compared with optimal blood pressure, the relative risk of CVD was 2.33 (1.85 to 2.92) for high-normal blood pressure and was 1.81 (1.47 to 2.22) for normal blood pressure among blacks.[19] An inverse association of optimal blood pressure and a positive association of Stage 1 hyper-

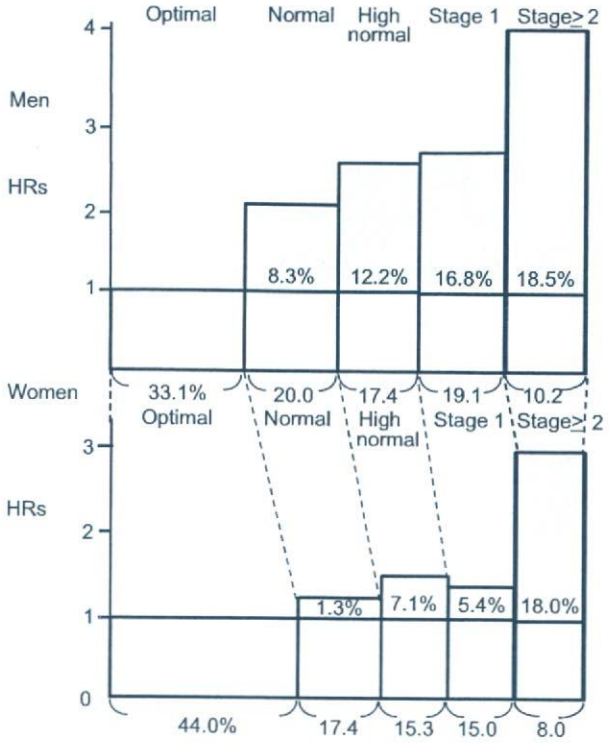

Figure. The HRs and positive fraction attributable to exposure to each blood pressure category (optimal, normal, and high-normal blood pressures and hypertension Stages 1 and ≥2) at baseline for CVD were estimated by sex. The gray area displays excessive incidence of CVD due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2.

tension with coronary heart disease were observed in men compared with normal blood pressure.[12] The Framingham Heart Study revealed that 17.6% and 37.3% of subjects with baseline normal and high-normal blood pressure, respectively, were diagnosed with hypertension within 4 years. High-normal blood pressure has also been associated with increased risk of carotid atherosclerosis,[20] altered cardiac morphological features,[21] and diastolic ventricular dysfunction,[22] all of which may be precursors of incidence of CVD.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al demonstrated a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan.[5] Sairenchi et al revealed that high-normal blood pressure was associated with an increased risk of CVD mortality in Japanese men.[23] The NIPPON DATA 80 also indicated that high blood pressure was a risk factor for mortality from all causes as well as death from CVD among Japanese.[24] All of these studies used end points of mortality. The risk of CVD incidence, like used in this study, is a more direct measure of CVD risk than is the risk of CVD mortality, which is heavily influenced by treatment.

In prospective studies examining the incidence of CVD in Japanese populations, the Ohasama study demonstrated that high-normal blood pressure was a risk factor for stroke by using homed blood pressure, but not by using causal blood pressure.[13] The Hisayama study, which observed the natural course of untreated hypertension in a general Japanese elderly population over a 32-year period, indicated that high-normal blood pressure was not a risk factor for cerebral infarction.[4] This cohort was approximately half the size of our cohort, and the subjects were older and observed for longer periods of time. Hypertensive risk for CVD decreased with advancing age.[25] Over very long periods, confounding factors, including advancing aging, menopause, lifestyle modifications, and medication, will affect blood pressure classification. The Tanno-Sobetu study determined that high-normal blood pressure, determined according to the 1999 World Health Organization/International Society of Hypertension criteria, was not a risk factor for CVD in comparison to optimal and normal blood pressures.[26]

In this study, we did not find an association between high-normal blood pressure and CVD incidence in women. The association between blood pressure category and coronary heart disease is well documented to be weaker in women than in men.[12] For each racial/ethnic group, the mean SBP and DBP values in men were 6 to 7 and 3 to 5 mm Hg higher, respectively, than the values in women.[27] Postmenopausal effects have been associated with elevated blood pressure.[28] Therefore, the period of hypertension exposure tends to be shorter in women than in men. The incidence of CVD was lower in women (3.9 per 1000 person-year) than in men (7.1 per 1000 person-years) in this study. The percentages of those with hypertension who were aware, treated, and controlled were higher for women than men.[27]Because the frequency of white coat hypertension is higher in women than in men,[29,30] blood pressure at baseline examination may be overestimated in women, which may result in the absence of an association between high-normal blood pressure and CVD incidence in women.

The multivariable HR of CVD incidence for normal blood pressure was 2-fold higher than that for optimal blood pressure. In the Honolulu heart program and the Puerto Rico heart health program, the multivariable HRs of CVD incidence for normal blood pressure were approximately 2-fold higher than those for optimal blood pressure.[12] Thus, lower blood pressure appears to prevent the incidence of CVD.

The crude 10-year cumulative incidences of CVD in this subjects who had optimal, normal, and high-normal blood pressure were approximately 2%, 6%, and 8% for men and 2%, 3%, and 5% for women, respectively (data not shown). In the Framingham Heart Study, those were 5%, 8%, and 10% for men and 1%, 3%, and 6% for women, respectively.[12] Compared with the Framingham Heart Study, the incidences of CVD for optimal blood pressure in the Suita study tend to be lower in men and similar in women.

Our study has several limitations. The primary limitation is a dilution bias[31]; this study was based on a single-day measurement of blood pressure, which may lead to a misclassification of blood pressure levels. Previous epidemiological evidence has suggested, however, that blood pressure measurements taken on a single day are accurate.[32] Second, approximately 10% of subjects who underwent baseline survey did not respond to our questionnaires thereafter. However, we found no clinical background difference be-