Table 3 Sex-specific and smoking status-stratified hazard ratios and 95% confidence intervals for cardiovascular disease mortality by healthy lifestyle score

	Healthy lifestyle score (points)						
	0–2	**3**	**4**	**5**	**6**	**7–8**	***P* for trend**
Men							
Person-years	35 054	51 100	66 549	61 279	38 429	17 695	
Stroke							
n	76	101	110	80	52	22	
Age-adjusted mortality rate	3.18	3.05	2.20	1.75	1.69	1.52	
Age-adjusted HR (95% CI)	1.00	0.85 (0.63–1.14)	0.63 (0.47–0.85)	0.45 (0.33–0.61)	0.44 (0.31–0.62)	0.35 (0.22–0.56)	<0.0001
Multivariable HR (95% CI)	1.00	0.85 (0.63–1.14)	0.64 (0.48–0.86)	0.45 (0.33–0.62)	0.46 (0.32–0.66)	0.36 (0.22–0.58)	<0.0001
Coronary heart disease							
n	33	41	69	62	30	5	
Age-adjusted mortality rate	1.33	1.12	1.44	1.35	1.07	0.31	
Age-adjusted HR (95% CI)	1.00	0.79 (0.50–1.26)	0.93 (0.62–1.41)	0.83 (0.54–1.26)	0.60 (0.37–0.99)	0.19 (0.07–0.49)	0.0008
Multivariable HR (95% CI)	1.00	0.80 (0.51–1.27)	0.94 (0.62–1.43)	0.84 (0.55–1.28)	0.62 (0.38–1.02)	0.19 (0.08–0.50)	0.0012
Total cardiovascular disease							
n	155	213	265	213	122	44	
Age-adjusted mortality rate	6.47	6.25	5.42	4.62	4.11	2.91	
Age-adjusted HR (95% CI)	1.00	0.88 (0.71–1.08)	0.75 (0.62–0.92)	0.59 (0.48–0.72)	0.51 (0.40–0.64)	0.34 (0.25–0.48)	<0.0001
Multivariable HR (95% CI)	1.00	0.88 (0.71–1.08)	0.76 (0.62–0.93)	0.59 (0.48–0.73)	0.52 (0.41–0.67)	0.35 (0.25–0.49)	<0.0001
	Healthy lifestyle score (except for smoking status)						
	0–1	**2**	**3**	**4**	**5**	**6–7**	***P* for trend**
Total cardiovascular disease							
Smokers							
Person-years	8659	22 001	37 661	39 612	26 592	12 009	
n	40	88	148	161	96	33	
Age-adjusted mortality rate	7.18	5.99	6.16	5.89	5.20	3.78	
Multivariable HR (95% CI)	1.00	0.88 (0.61–1.28)	0.84 (0.60–1.20)	0.81 (0.57–1.14)	0.68 (0.47–0.98)	0.54 (0.34–0.85)	0.001
Non-smokers							
Person-years	4394	13 438	26 937	34 688	28 203	15 912	
n	27	65	104	117	92	41	
Age-adjusted mortality rate	7.65	6.15	4.64	4.08	4.00	2.98	
Multivariable HR (95% CI)	1.05 (0.64–1.71)	0.77 (0.52–1.15)	0.59 (0.41–0.86)	0.48 (0.34–0.69)	0.47 (0.32–0.67)	0.33 (0.21–0.51)	<0.0001

Women							
Person-years	4460	21 463	58 207	96 888	103 246	74 934	
Stroke							
n	14	51	93	109	103	38	
Age-adjusted mortality rate	3.81	2.66	2.21	1.84	1.95	1.01	
Age-adjusted HR (95% CI)	1.00	0.63 (0.35–1.13)	0.52 (0.30–0.92)	0.43 (0.25–0.76)	0.42 (0.24–0.74)	0.24 (0.13–0.44)	<0.0001
Multivariable HR (95% CI)	1.00	0.68 (0.37–1.23)	0.57 (0.32–1.00)	0.48 (0.27–0.84)	0.48 (0.27–0.84)	0.28 (0.15–0.53)	<0.0001
Coronary heart disease							
n	8	19	42	41	34	18	
Age-adjusted mortality rate	2.28	1.00	1.01	0.60	0.59	0.54	
Age-adjusted HR (95% CI)	1.00	0.41 (0.18–0.93)	0.41 (0.19–0.87)	0.28 (0.13–0.59)	0.24 (0.11–0.51)	0.19 (0.08–0.44)	<0.0001
Multivariable HR (95% CI)	1.00	0.42 (0.18–0.97)	0.42 (0.19–0.89)	0.29 (0.14–0.63)	0.25 (0.11–0.54)	0.20 (0.09–0.47)	<0.0001
Total cardiovascular disease							
n	33	106	204	249	222	81	
Age-adjusted mortality rate	9.19	5.57	4.85	4.17	4.00	2.28	
Age-adjusted HR (95% CI)	1.00	0.55 (0.37–0.81)	0.48 (0.34–0.70)	0.42 (0.29–0.60)	0.39 (0.27–0.56)	0.22 (0.14–0.32)	<0.0001
Multivariable HR (95% CI)	1.00	0.58 (0.39–0.86)	0.51 (0.35–0.74)	0.45 (0.31–0.65)	0.42 (0.29–0.60)	0.24 (0.16–0.36)	<0.0001
	Healthy lifestyle score (except for smoking status)						
	0–1	**2**	**3**	**4**	**5**	**6–7**	***P* for trend**
Total cardiovascular disease							
Smokers							
Person-years	251	1558	3799	4799	3712	2103	
n	5	12	14	18	9	6	
Age-adjusted mortality rate	26.31	10.01	5.25	6.23	5.34	5.91	
Multivariable HR (95% CI)	1.00	0.27 (0.09–0.78)	0.12 (0.04–0.34)	0.15 (0.06–0.40)	0.13 (0.04–0.39)	0.20 (0.06–0.69)	0.02
Non-smokers							
Person-years	2650	17 663	53 408	93 176	101 378	74 699	
n	16	92	186	240	216	81	
Age-adjusted mortality rate	9.19	5.57	4.85	4.17	4.00	2.28	
Multivariable HR (95% CI)	0.18 (0.07–0.49)	0.14 (0.06–0.35)	0.12 (0.05–0.29)	0.11 (0.04–0.26)	0.10 (0.04–0.24)	0.06 (0.02–0.14)	<0.0001

Multivariable adjustment: age, history of hypertension, history of diabetes, education level, regular employment, and perceived mental stress.

The followings are our study limitations. First, the baseline data were obtained at one time point only. Because of the possible changes in lifestyle over the follow-up period, non-differential measurement errors would have attenuated the observed associations, and the real associations might be stronger. Second, we used mortality data rather than incidence as the endpoint; episodes of CVD and/or other diseases may induce lifestyle changes and consequently mortality risk in some individuals. To reduce this effect at most, we excluded those with a history of stroke, CHD, and cancer at baseline, and excluded early deaths at baseline for the secondary analysis. Third, there might be a concern about selection bias as we excluded 61 918 participants who had missing information. The exclusion of these individuals, however, was unlikely to influence the relationships, since these baseline characteristics did not differ substantially from the rest of the cohort.

In conclusion, the number of baseline healthy lifestyle behaviours was inversely associated with the risk of mortality from CVD. Mortality risk from stroke, CHD, and total CVD in the highest healthy lifestyle score category was one-third among men and one-fourth among women, compared with those of the lowest score category. The inverse association among men was more evident for non-smokers than for smokers. These results suggest a large role of lifestyle modification in the prevention of CVD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Aldosterone-to-renin ratio and nocturnal blood pressure decline in a general population: the Ohasama study

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Background Aldosterone-to-renin ratio (ARR) is an index for inappropriate aldosterone activity and salt sensitivity. We previously reported that elevated ARR might be associated with salt-sensitive hypertension. Because salt-sensitive hypertensive patients are reported to show a diminished nocturnal decline in blood pressure, we hypothesized that high ARR may be associated with diminished nocturnal decline in blood pressure (generally referred to as a 'nondipping' pattern), especially in individuals with high sodium intake.

Methods This study tested this hypothesis in 184 participants aged at least 55 years not receiving antihypertensive treatment in a general Japanese population (age: 67.6 ± 6.9 years; 71.7% women).

Results Ambulatory blood pressure monitoring identified 63 (34.2%) participants with a nondipping pattern (nocturnal decline of SBP <10%). The median plasma renin activity (PRA), plasma aldosterone concentration (PAC), and ARR were 0.8 ng/ml per h, 8.3 ng/dl, and 8.7 ng/dl per (ng/ml per h), respectively. After adjustment for possible confounding factors, each 1 SD increase in logARR was associated with the prevalence of nondipping pattern (odds ratio, 1.95; $P = 0.002$). This association was observed in individuals in the highest tertile of 24-h urinary sodium excretion estimated from spot urine data (e24-hUNa; ≥179.6 mEq/day; $P = 0.01$) but disappeared in those in the lowest tertile of e24-hUNa (<147.9 mEq/day; $P = 0.6$). In those in the highest tertile of e24-hUNa, PRA was significantly lower in nondippers than in dippers (0.49 vs. 0.85 ng/ml per h) despite no differences in PAC.

Conclusion These results suggest that relative aldosterone excess might be related to a nondipping pattern of blood pressure, especially in individuals with high sodium intake. *J Hypertens* 29:1940–1947 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: aldosterone-to-renin ratio, nondipping pattern, relative aldosterone excess, salt-sensitive hypertension, sodium intake

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; ARR, aldosterone-to-renin ratio; BP, blood pressure; CVD, cardiovascular disease; e24-h-UK, estimated 24-h urinary potassium excretion; e24-h-UNa, estimated 24-h urinary sodium excretion; eGFR, estimated glomerular filtration rate; IDH, isolated daytime hypertension; INH, isolated night-time hypertension; OR, odds ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activities; SHT, sustained hypertension

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Introduction

Aldosterone-to-renin ratio (ARR) is believed to be more reproducible than aldosterone levels alone and could be an index for inappropriate aldosterone activity and salt sensitivity [1,2]. A few population studies based solely on office (conventional) blood pressure (BP) measurements have reported on the association of ARR with hypertension [3,4]. The Framingham Heart study demonstrated the clinical and genetic correlates of ARR and relations to BP in a large community-based sample [3]. Recently, we reported that elevated ARR levels were associated with hypertension [5]. Moreover, we also demonstrated that the association of ARR with hypertension was strengthened for individuals with high sodium intake, whereas it was less remarkable for those with low sodium intake [5]. These results suggest that elevated ARR might be related to salt-sensitive hypertension. In addition, Uzu *et al.* [6,7] reported a diminished nocturnal BP fall, which is generally referred to as a 'nondipping' pattern, in patients with salt-sensitive hypertension. Therefore, we hypothesized that, especially in individuals with high sodium intake, high ARR would be associated with a nondipping pattern. One previous study examined the association between ARR and ambulatory BP. However, that study was conducted in a special population (hypertensive or hyperlipidemic sib pairs). Furthermore, it did not report the association of ARR and a nondipping pattern [8]. The objective of this

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cross-sectional study was to clarify whether ARR was associated with a nondipping pattern in relation to sodium intake in a general Japanese population.

Methods

Design

This investigation was a part of the Ohasama study. Socioeconomic and demographic characteristics of this region and details of the study project have been described previously [9,10]. The Institutional Review Boards of Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study.

Study population

The population of Ohasama in 1998 was 7202. Of those, 3077 were aged 55 years or older. Individuals ($n = 492$) who were not at home during the normal working hours of the study nurses, and those who were hospitalized, mentally ill, or bedridden ($n = 185$), were not eligible for inclusion. Of the remaining 2400 eligible individuals, 1270 (53%; mean age, 68.9 ± 6.4 years; 65% women) gave informed consent and participated in the ambulatory BP monitoring study. Among those, 510 (mean age, 68.6 ± 7.1 years; 65% women) participated in the study to measure biomarkers including plasma aldosterone concentration (PAC) and plasma renin activity (PRA). For the current analysis, we further excluded 232 individuals treated with antihypertensive drugs because of the effects of antihypertensive medications on the renin–angiotensin system and circadian BP variation [11]. Ninety participants were also excluded because they had missing values for urinary sodium excretion from spot urine. To exclude possible patients with primary aldosteronism, we further excluded four participants who had ARR at least 20 ng/dl per (ng/ml per min) in the presence of PAC at least 15 ng/dl, which was the cut-off value to screen for primary aldosteronism [12,13]. After applying these exclusions, 184 participants were included in the present study.

Blood pressure measurements

Ambulatory BP was monitored using a fully automatic FM-800 device (Fukuda Denshi Co., Ltd., Tokyo, Japan) [14] preset to measure BP every 30 min. The device was attached by well trained public health nurses who visited the participants' homes on a weekday morning and detached the device the next morning. According to the diary, 'daytime' and 'night-time' were determined as the waking and sleeping periods of the participant, respectively. Artifactual measurements during recordings were defined according to previously described criteria [15] and were omitted from the analysis. Office BP was measured twice consecutively in the sitting position, after a minimum 2-min rest interval; measurements were made by a doctor or technicians at local medical centers using an automatic device (HEM-9000AI; Omron Healthcare Co., Ltd., Kyoto, Japan) based on the oscillometric method as used in HEM-907 (Omron Healthcare Co., Ltd.) [16,17]. The mean of the two brachial BP measurements was defined as the office BP. We defined 24-h hypertension as a 24-h ambulatory BP at least 130 mmHg systolic or at least 80 mmHg diastolic, daytime hypertension as a daytime BP of at least 135/85 mmHg, and night-time hypertension as a night-time BP of at least 120/70 mmHg [18,19]. On the basis of these cut-off limits of ambulatory BP, participants were classified into four groups: normotensive individuals during daytime and night-time; participants with isolated daytime hypertension; participants with isolated night-time hypertension; and participants with hypertension sustained during daytime and night-time. A nondipping pattern was defined as a nocturnal reduction of systolic ambulatory BP less than 10% [20].

Data collection

Blood for measurement of PRA (ng/ml per h) and PAC (ng/dl) was drawn from participants in a sitting position after approximately 30-min rest, between 0900 and 1100 h or between 1300 h and 1500 h; most participants had not fasted. Blood was collected in chilled EDTA tubes and measured by radioimmunoassay (SRL, Tokyo, Japan) with the SPAC-S Aldosterone Kit (TFB, Tokyo, Japan) for PAC and with the PRA 'TFB' (TFB) for PRA. The values of interassay and intra-assay variations and lower limits of detections of PRA and PAC are reported elsewhere [5,21]. Hypercholesterolemia was defined as total cholesterol at least 5.68 mmol/l (≥220 mg/dl), use of medication for hypercholesterolemia, and/or a history of hypercholesterolemia. Diabetes mellitus was defined as a fasting blood glucose level at least 7.0 mmol/l (≥126 mg/dl), random blood glucose level at least 11.11 mmol/l (≥200 mg/dl), HbA1c level at least 6.5%, use of medication for diabetes, and/or a history of diabetes mellitus. From data on spot urine, we estimated 24-h urinary sodium (e24-hUNa) and potassium (e24-hUK) excretion using the following formula [22,23]: estimated 24hUNa (or e24-hUK) (mEq/day) = 21.98 × [sodium (or potassium) concentration in spot urine (mEq/l)/creatinine concentration in spot urine (mg/l) × estimated 24-h urinary creatinine (e24-hUCr, mg/day)]$^{0.392}$. Estimated 24-hUCr = −2.04 × age + 14.89 × body weight (kg) + 16.14 × height (cm) − 2244.45.

Statistical analysis

PRA, PAC, and ARR were natural-log transformed because of their positively skewed distributions. To analyze the relationship between tertiles of ARR and participant characteristics, we compared means and proportions using analysis of variance (ANOVA) and the χ^2 test for univariate analysis. Using multiple logistic analyses, we examined the association of PRA, PAC, and ARR with hypertension after adjustment for sex, age, BMI, current drinking and smoking status,

hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, and serum sodium concentration. In addition to these covariates, we further adjusted for 24-h SBP level when we examined the association between ARR and a nondipping pattern. We also determined the significance of the interaction between e24-hUNa and PRA, PAC, or ARR by adding an interaction variable to the logistic regression model. Using multiple linear regression analyses, we evaluated the correlates of logARR with several clinical parameters and determined which measurement of BP was more strongly associated with ARR. Differences in PRA, PAC, and ARR among the BP groups were established by analysis of covariance (ANCOVA) with Tukey's multiple comparison tests. Data are expressed as mean ± SD unless otherwise noted. SAS version 9.1 software (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

Results

Participant characteristics

The 184 participants included 132 women (71.7%). Mean values were 67.6 ± 6.9 years for age, 23.5 ± 3.1 kg/m^2 for BMI, 5.48 ± 0.80 mmol/l for total cholesterol level, 164.1 ± 37.8 mEq/day for e24-hUNa excretion level (salt equivalent, 9.6 g/day), and 38.9 ± 6.9 mEq/day for e24-hUK excretion level. At enrollment, 13 (7.1%) participants were current smokers, 77 (41.8%) were current drinkers, 98 (53.3%) had hypercholesterolemia, 34 (18.5%) had diabetes mellitus, and 15 (8.2%) had a history of cardiovascular disease. The mean systolic/diastolic 24-h, daytime, and night-time BP values of participants were 126.2 ± 12.3/79.1 ± 7.7 mmHg, 131.9 ± 13.6/82.9 ± 8.5 mmHg, and 115.4 ± 13.9/71.6 ± 8.4 mmHg, respectively. The median values (25–75th percentiles) were 0.8 (0.5–1.5) ng/ml per h for PRA, 8.3 (6.0–10.9) ng/dl for PAC, and 8.7 (5.5–15.8) ng/dl per (ng/ml per h) for ARR. Table 1 shows characteristics of participants among the tertiles of ARR. We analyzed the multivariable clinical correlates of logARR using a multiple regression model, including logARR as the dependent variable and sex, age, BMI, drinking, smoking, hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, serum sodium concentration, and e24-hUNa as independent variables. Female sex [standardized regression coefficients (β) = 0.35, $P < 0.0001$], BMI ($\beta = 0.16$, $P = 0.02$), and serum sodium concentration ($\beta = 0.36$, $P < 0.0001$) were positively associated with logARR, and hypercholesterolemia ($\beta = -0.15$, $P = 0.02$) was negatively associated with logARR.

Associations of log aldosterone-to-renin ratio, log plasma renin activity, or log plasma aldosterone concentration with the prevalence of hypertension

Table 2 shows the association of logPRA, logPAC, and logARR with the prevalence of hypertension. Of the 184 study participants, 94 (51.1%) had 24-h hypertension,

Table 1 Clinical characteristics among groups classified by tertiles of aldosterone-to-renin ratio

	Tertiles of ARR (ng/dl per ng/ml per h)			
Characteristics	<6.6 ($n = 61$)	6.6–12.4 ($n = 61$)	≥12.4 ($n = 62$)	P
Female, *n* (%)	38 (62.3)	42 (68.9)	52 (83.9)	0.02
Age (years)	67.6 ± 6.9	67.7 ± 7.4	67.6 ± 6.4	1.0
BMI (kg/m^2)	22.9 ± 2.9	24 ± 3.4	23.7 ± 3	0.1
Past history of CVD, *n* (%)	6 (9.8)	5 (8.2)	4 (6.5)	0.8
Diabetes, *n* (%)	9 (14.8)	16 (26.2)	9 (14.5)	0.2
Hypercholesterolemia, *n* (%)	37 (60.7)	33 (54.1)	28 (45.2)	0.2
Smoking, *n* (%)	4 (6.6)	3 (4.9)	6 (9.7)	0.6
Drinking, *n* (%)	22 (36.1)	28 (45.9)	27 (43.5)	0.5
Biochemical measurements				
HbA1c (%)	5.4 ± 0.5	5.5 ± 0.6	5.4 ± 0.4	0.5
Total cholesterol (mmol/l)	5.57 ± 0.84	5.56 ± 0.63	5.30 ± 0.77	0.1
eGFR (ml/min per 1.73 m^2)	78.8 ± 15	81 ± 14.6	76.4 ± 15.1	0.2
Serum sodium (mEq/l)	141.0 ± 1.5	141.8 ± 1.4	142.2 ± 1.4	<0.0001
Serum potassium (mEq/l)	4.3 ± 0.4	4.3 ± 0.3	4.3 ± 0.3	0.9
e24-h-UNa excretion (mEq/day)	139.9 ± 49.5	144.9 ± 48.3	141.0 ± 39.9	0.1
e24-h-UK excretion (mEq/day)	38.7 ± 6.6	40.3 ± 7.9	37.7 ± 6.1	0.1
24-h BP				
Systolic (mmHg)	122.1 ± 11.7	126.8 ± 11.8	129.7 ± 12.4	0.003
Diastolic (mmHg)	77.5 ± 7.0	78.3 ± 7.9	81.3 ± 7.8	0.02
Daytime BP				
Systolic (mmHg)	128.6 ± 13.4	132 ± 13.2	134.9 ± 13.7	0.03
Diastolic (mmHg)	81.8 ± 7.9	81.9 ± 8.8	85 ± 8.5	0.06
Night-time BP				
Systolic (mmHg)	110.4 ± 12.9	116.5 ± 13.7	119.3 ± 13.9	0.001
Diastolic (mmHg)	69.6 ± 7.7	71.2 ± 8.4	73.8 ± 8.7	0.02
Office BP				
Systolic (mmHg)	131.2 ± 14.4	133.7 ± 15.8	138.2 ± 17.8	0.05
Diastolic (mmHg)	73.4 ± 8.8	71.7 ± 10.2	77.0 ± 10.5	0.01

Estimated glomerular filtration rate (eGFR) was estimated from the serum creatinine value using a Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × age$^{-0.287}$ × serum Cr$^{-1.094}$ (if woman × 0.739). e24-h-UNa (UK), estimated 24-h urinary sodium (or potassium) excretion by the calculation formula based on spot urine data [21,22] (for further details, see method). ARR, aldosterone-to-renin ratio; BP, blood pressure; CVD, cardiovascular disease.

Table 2 Odds ratios (95% confidence intervals) for prevalence of hypertension per 1 SD increase in log plasma renin activity, log plasma aldosterone concentration, and log aldosterone-to-renin ratio

	24-h hypertension ($N=94$)	Daytime hypertension ($N=93$)	Night-time hypertension ($N=115$)	Office hypertension ($N=67$)
Age and sex adjustment				
logPRA	0.58 (0.41–0.81)†	0.72 (0.52–0.99)*	0.58 (0.40–0.83)†	0.60 (0.42–0.85)*
logPAC	1.21 (0.89–1.65)	1.16 (0.85–1.57)	1.13 (0.82–0.57)	0.95 (0.67–1.30)
logARR	1.96 (1.39–2.77)‡	1.52 (1.10–2.10)*	1.87 (1.31–2.68)‡	1.64 (1.16–2.31)*
Full adjustment				
logPRA	0.57 (0.39–0.85)†	0.75 (0.52–1.09)	0.53 (0.35–0.82)†	0.64 (0.43–0.95)*
logPAC	1.20 (0.86–1.67)	1.17 (0.84–1.62)	1.15 (0.81–1.63)	0.93 (0.66–1.29)
logARR	2.00 (1.34–2.98)‡	1.48 (1.01–2.15)*	2.07 (1.36–3.14)‡	1.48 (1.01–2.17)*

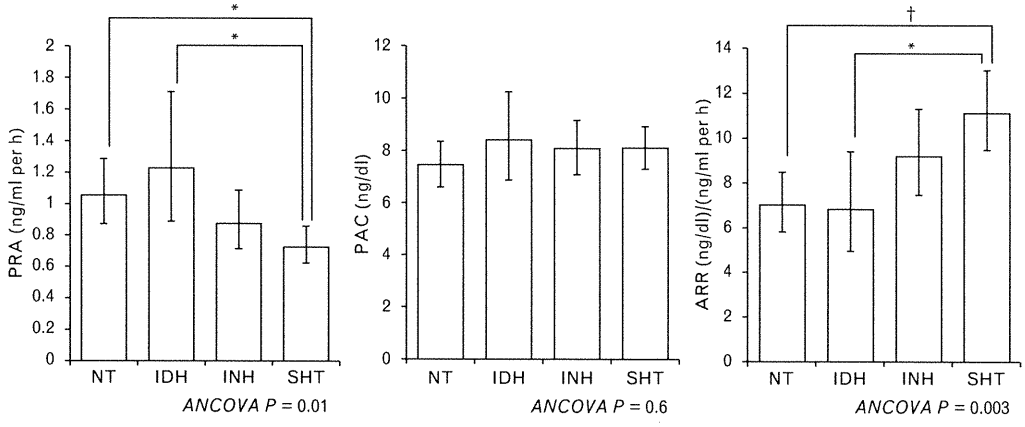
Full adjustment model was adjusted for sex, age, BMI, habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, past history of cardiovascular disease, serum sodium, and e24-h U sodium excretion. The 24-h hypertension, daytime, night-time hypertension, and office hypertension were at least 130/80, 135/85, 120/70, and 140/90 mmHg, respectively. ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity. *$P<0.05$. †$P<0.01$. ‡$P<0.001$.

93 (50.5%) had daytime hypertension, and 115 (62.5%) had night-time hypertension. After adjustment for possible confounding factors, we observed a significant association of logARR and logPRA with hypertension except for the relation between logPRA and daytime hypertension. However, logPAC was not related to hypertension ($P \geq 0.2$).

We then classified the participants into four groups according to their ambulatory BP profile (Fig. 1). Among the 184 study participants, 51 (27.7%) had normotension, 18 (9.8%) had isolated daytime hypertension, 40 (21.7%) had isolated night-time hypertension, and 75 (40.8%) had sustained hypertension. Participants with sustained hypertension had significantly higher ARR and lower PRA than those with normotension ($P=0.03$ for PRA, $P=0.004$ for ARR) and those with isolated daytime hypertension ($P=0.03$ for PRA, $P=0.048$ for ARR). Participants with isolated night-time hypertension tended to have relatively higher ARR.

To compare daytime BP and night-time BP in terms of predictive power of ARR, we performed a multiple regression model including logARR as the dependent variable and daytime BP levels, night-time BP levels, and other confounding factors as independent variables. LogARR was predicted by night-time BP levels ($P=0.0005$ for SBP, $P=0.002$ for DBP), but not by daytime BP levels ($P=0.4$ for SBP, $P=0.3$ for DBP). Similarly, when we included 24-h BP and office BP as the independent variables instead of daytime BP and night-time BP, logARR was predicted only by 24-h BP levels ($P \leq 0.0007$ for 24-h BP, $P \geq 0.6$ for office BP).

Fig. 1



Means of plasma renin activity, plasma aldosterone concentration, and aldosterone-to-renin ratio among four groups according to ambulatory blood pressure profile. Means (95% confidence intervals) of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and aldosterone-to-renin ratio (ARR) after adjusting for sex, age, BMI, habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and serum sodium level. Participants were classified into four groups as follows: normotension (NT, $n=51$), daytime blood pressure (BP) less than 135/85 mmHg and night-time BP less than 120/70 mmHg; isolated daytime hypertension (IDH, $n=18$), daytime BP at least 135/85 mmHg and night-time BP less than 120/70 mmHg; isolated night-time hypertension (INH, $n=40$), daytime BP less than 135/85 mmHg and night-time BP at least 120/70 mmHg; sustained hypertension (SHT, $n=75$) daytime BP at least 135/85 mmHg and night-time BP at least 120/70 mmHg. *$P<0.05$, †$P<0.01$.

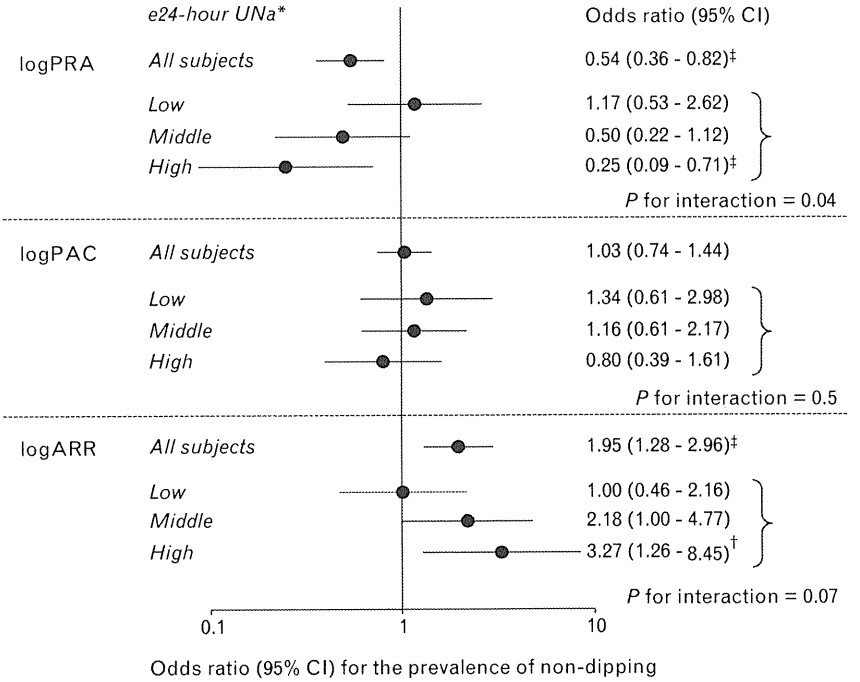
Associations of log plasma renin activity, log plasma aldosterone concentration, or log aldosterone-to-renin ratio with nondipping pattern by tertiles of e24-h urine sodium excretion

In all participants, each 1 SD increase in logARR was significantly associated with the prevalence of a nondipping pattern ($n = 63$, 34.3%) even after further adjustment for 24-h SBP level ($P = 0.002$; Fig. 2). LogPRA was inversely associated with the prevalence of a nondipping pattern ($P = 0.003$). Then, we stratified participants by tertiles of e24-hUNa excretion (low <147.9, middle 147.9–179.6, and high ≥179.6 mEq/day; Fig. 2). The association of ARR with a nondipping pattern remained in participants in the high tertile of e24-hUNa (≥179.6 mEq/day; $P = 0.01$) but disappeared in those in the low tertile of e24-hUNa (<147.9 mEq/day; $P = 1.0$). There were significant or marginally significant interactions between tertiles of e24-hUNa excretion and logPRA (P for interaction = 0.04) or logARR (P for interaction = 0.07) on the prevalence of a nondipping pattern. LogPAC was not associated with a nondipping pattern in any stratum of e24-hUNa. In participants in the high tertile of e24-hUNa excretion, nondippers ($n = 22$) had significantly lower PRA and higher ARR than dippers ($n = 40$) after adjustment for confounding factors (Fig. 3). In contrast, when a nondipping pattern was defined by DBP, we found no significant association of ARR with a nondipping pattern (data not shown). We also performed stratified analyses by tertiles of e24-hUK (<35.9, 35.9–41.6, and ≥41.6 mEq/day), sex (male/female), age (<65/≥65 years), and BMI (<25/≥25 kg/m^2). These stratifications did not significantly affect the associations of logARR with the prevalence of a nondipping pattern ($P \geq 0.2$ for all interactions).

Discussion

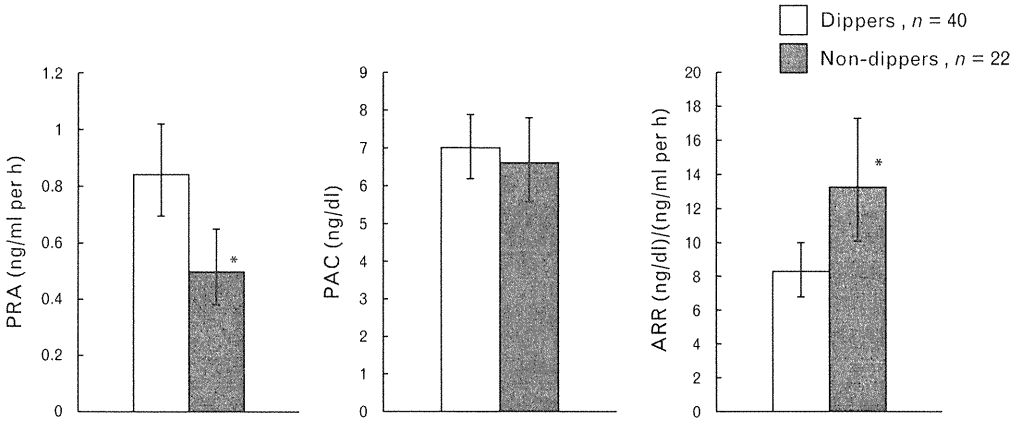
In the present cross-sectional study, we demonstrated a significant association between ARR and the prevalence of a nondipping pattern in a general population, especially in individuals with the highest tertile of 24-hUNa, after adjusting for sex, age, BMI, current smoking and drinking status, hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, serum sodium levels, and 24-h SBP. We also found that elevated ARR was significantly associated with the prevalence of 24-h, daytime, or night-time hypertension. The association of night-time BP with ARR was stronger than those with daytime BP. Individuals with sustained hypertension had

Fig. 2



Adjusted odds ratios (95% confidence intervals) for the prevalence of a nondipping pattern per 1 SD increase in log plasma renin activity, log plasma aldosterone concentration, and log aldosterone-to-renin ratio by tertiles of e24-h urine sodium excretion. All models were adjusted for sex, age, BMI, habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, serum sodium, and 24-h SBP. A total of 20, 21, and 22 participants were nondippers among subgroups with low (<147.9 mEq/day, $n = 61$), middle (147.9–179.8 mEq/day, $n = 61$), and high (≥179.8 mEq/day, $n = 62$) e24-h urine sodium excretion, respectively. *e24-h-UNa, estimated 24-h urinary sodium excretion by the calculation formula based on spot urine data [22,23] (for further details, see methods). ARR, aldosterone-to-renin ratio; PAC, plasma aldosterone concentration; PRA, plasma renin activity. †$P < 0.05$. ‡$P < 0.01$.

Fig. 3



Plasma renin activity, plasma aldosterone concentration, and aldosterone-to-renin ratio in dippers and nondippers within the high e24-h urinary sodium excretion group. Means (95% confidence intervals) of plasma renin activity (PRA), plasma aldosterone concentration (PAC), and aldosterone-to-renin ratio (ARR) in a subgroup of participants with high e24-h urinary sodium excretion (>179.8 mEq/day) after adjusting for sex, age, BMI, habitual smoking, habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and serum sodium level. *ANCOVA $P < 0.01$ vs. dippers.

significantly higher ARR compared with those not only with normotension but also with isolated daytime hypertension.

We observed significant associations of ARR with female sex [3,5], BMI [5,24], serum sodium [5], and nonhypercholesterolemia [21]; these findings are consistent with previous reports [3,5,21,24].

Our findings extend the validation of the relationship between ARR and a nondipping pattern from patients with hyperaldosteronism [25] or resistant hypertension [25] to a general population. This study demonstrated for the first time the association of elevated ARR with an increased prevalence of a nondipping pattern in a general population. Furthermore, whereas the association of ARR with a nondipping pattern was observed in individuals in the high tertile of e24-hUNa, it became nonsignificant for those in the low tertile of e24-hUNa (Fig. 2). In individuals in the high tertile of e24-hUNa excretion group, despite no differences in PAC, nondippers had a significantly lower PRA than dippers (Fig. 3). As discussed previously [21], such form of low renin and normal aldosterone is called relative aldosterone excess (or low-renin hypertension), which might be responsible for salt-sensitive hypertension due to inappropriate sodium and fluid retention or impaired nitric oxide-mediated vasodilation [26,27]. Uzu *et al.* [6] described that nocturnal BP decline was diminished in salt-sensitive essential hypertensive patients with high salt intake. In line with these previous studies [5,6,21], the findings of our present analysis suggest that salt sensitivity may play a role in the association of high ARR with a nondipping pattern. We consider that one of the mechanisms of this may involve enhanced sodium excretion during the night-time due to sodium retention during the daytime due to relative aldosterone excess, as it is reported that the night/day ratio of sodium excretion was higher in essential hypertensive patients who were nondippers than in those who were dippers [28]. Because previous studies have shown the predictive power of high salt sensitivity [29] or diminished nocturnal BP decline [30] for cardiovascular mortality, the present study suggests that elevated high ARR, that is, relative aldosterone excess, may be linked to an increased risk of cardiovascular disease in individuals with high salt intake and suggests that salt reduction can potentially weaken the deleterious effects of high ARR on circadian BP variation. However, this study was cross-sectional, and thus cause-and-effect relations of these observations cannot be made. One could also hypothesize that high sodium intake simply strengthened the association between ARR and a nondipping pattern because salt loading can enhance the screening accuracy of ARR for primary aldosteronism [2]. Prospective studies are needed to elucidate the associations among ARR, nondipping, salt intake, and the future risk of cardiovascular disease.

ARR was associated not only with night-time hypertension but also with daytime hypertension. Moreover, individuals with sustained hypertension had higher ARR than those with normotension or daytime hypertension. A recent study with large sample size showed that sustained hypertension had the highest risk of all cardiovascular events among the four groups classified according to the same criteria used in Fig. 1 [31]. Thus, the

association of ARR with sustained hypertension probably highlights that ARR is strongly involved in the high prevalence of hypertension as well as a nondipping pattern and provides further support for the hypothesis that high ARR may enhance the risk of cardiovascular disease in a general population.

The present study indicated that 24-h BP levels are more closely associated with ARR levels than two measurements of office BP at one visit. Pimenta *et al.* [25] reported that 24-h BP levels were higher in patients with resistant hypertension than those without resistant hypertension, although there were no differences in office BP levels. We also previously reported that ARR was more closely related to hypertension diagnosed by home BP measurements than by office BP measurements [5]. These stronger associations of ambulatory or home BP measurements with ARR than those of office BP measurements can be explained by the fact that out-of-office BP measurements eliminate the white-coat effect [9,32], offer more prognostic significance than office BP measurements [33,34], and are more indicative of target organ damage [35,36].

We could not find any significant associations between ARR and a diastolic nondipping pattern. One possible reason for this could be that DBP decreases with age after the sixth decade of life due to increased arterial stiffness, whereas SBP continuously increases [37], and the present study population was rather old.

The present study has several limitations. First, in the present study, we did not collect data on sodium intake from the food-frequency questionnaire used in our previous study [5]. Furthermore, we did not measure 24-h urinary sodium excretion. However, we estimated 24-h urinary sodium excretion using the formula [22,23] validated in the INTERSALT (INTERnational study on SALT and blood pressure) study in which 24-h urinary sodium excretion was rigorously measured. Thus, the present findings will remain largely consistent even if we use actual 24-h urinary sodium excretion instead of e24-hUNa. Second, participants underwent blood sampling between 0900 and 1100 h or between 1300 and 1500 h and most often had not fasted. These nonstandardized conditions of blood sampling could lead to a bias toward the null association of PAC to BP correlates, as PAC and PRA are affected by circadian variations, renal blood flow changes due to posture changes, and sodium intake [38]. However, it is difficult to collect blood samples under standardized conditions at the time of health check-ups when screening a large number of participants. Our findings in the present study might imply that, even when measured under nonstandardized conditions, ARR is a clinically useful index of relative aldosterone excess or salt sensitivity. Third, the study population predominantly included elderly and female individuals (mean age, 68.9 ± 6.4 years; 65% women). These imbalances might, to some extent, limit the external validity of the findings. Fourth, we did not have information about adrenocorticotropic hormone, mineralocorticoid hormones other than PAC, urinary excretion of aldosterone, or these metabolites. Fifth, because some patients with primary aldosteronism have a low renin level but a normal aldosterone level, we cannot exclude the possibility that primary aldosteronism was present in nondippers with the high tertile of e24-hUNa excretion.

In conclusion, the present study provides evidence for relative aldosterone excess contributing to night-time hypertension and a nondipping pattern, especially for individuals with high urinary sodium excretion. These results suggest that, in a general population, relative aldosterone excess (or low-renin hypertension) contributes to salt-sensitive hypertension. Our observational study was unable to resolve the issue whether salt reduction would weaken these deleterious effects of relative aldosterone excess. The answer to this question must await large-scale, randomized trials of the effects of salt restriction on a nondipping pattern in individuals with relative aldosterone excess.

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Conflicts of interest

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ORIGINAL ARTICLE

High fruit intake is associated with a lower risk of future hypertension determined by home blood pressure measurement: the OHASAMA study

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We investigate associations of fruit and vegetable intake with the risk of future hypertension using home blood pressure in a general population from Ohasama, Japan. We obtained data from 745 residents aged ⩾35 years without home hypertension at baseline. Dietary intake was measured using a validated 141-item food frequency questionnaire, and subjects were then divided into quartiles according to the fruit and vegetable intake. Home hypertension was defined as home systolic/diastolic blood pressure of ⩾135/85 mm Hg and/or the use of antihypertensive medication. During a 4-year follow-up period, we identified 222 incident cases of home hypertension. After adjustment for all putative confounding factors, the highest quartile of fruit intake was associated with a significantly lower risk of future home hypertension (odds ratio 0.40, 95% confidence interval 0.22–0.74, $P=0.004$). In conclusion, this study, based on home blood pressure measurement, suggests that higher intake of fruit is associated with a lower risk of future home hypertension.
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Keywords: fruit intake; vegetable intake; nutrition; home blood pressure; home hypertension; healthy community resident

Introduction

Hypertension is a major cause of morbidity and mortality,[1] with many studies indicating it to be significantly associated with an increased risk of cardiovascular disease (CVD) events.[2,3]

For several decades, researchers have mainly focused on the potentially adverse or preventive effects of various dietary factors.[4–16] Among these, fruit and vegetable intake has a especially powerful association with lower blood pressure (BP), and was found to reduce the risk of hypertension.[4–7] Our previous study using self-measured BP at home (home BP) found a significant cross-sectional association between intake of fruit and risk of hypertension.[17] However, although most studies exclude subjects who report a dietary change resulting from a diagnosis, the cross-sectional studies cannot remove subjects who change their diet after the diagnosis of hypertension.

Furthermore, in the majority of these studies, the definition of hypertension was based on conventional BP measurements. Because of the white-coat effect, a condition characterized by an elevated BP reading in a medical setting, these studies often overestimate the risk of high BP.[18] On the other hand, home BP measurements enable researchers to obtain multiple measurements over a long observation period under relatively controlled conditions.[19–22] The main strength of home BP is that it is not influenced by observer and regression dilution biases or the white-coat effect. Because of these benefits, home BP measurements are now

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considered a more accurate and reliable way of reflecting target organ damage and the prognosis of CVD when compared with conventional BP measurement taken in a medical setting,[19–22] and are also recommended in several general hypertension guidelines.[23,24]

Moreover, as there are geographical differences in the types of food intake and risk factors among countries,[25,26] it is important to confirm the reproducibility of previous findings of associations between BP and food and nutrient components in each population.

The aim of this study was to examine the association of fruit and vegetable intake with the risk of hypertension diagnosed by home BP during 4 years of follow-up in a Japanese general population.

Subjects and methods

Design

This study was part of the Ohasama study, a longitudinal community-based observational study of individuals who have participated in a home BP measurement project in Ohasama, Iwate prefecture, Japan. The geographic and demographic characteristics of the study subjects have been reported previously.[19,27]

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. Subjects provided written informed consent to participate.

Study population

In 1998, there were 5081 individuals aged $\geqslant 35$ years in Ohasama. Of the 4628 who answered the questionnaire (response rate 91.1%), 1820 subjects took part in home BP measurement; these individuals collected their own BP data on at least 3 days during the 4-week measurement period in 1998. Among those, people who had home hypertension at baseline ($n=394$) and those who died ($n=43$) or moved away from the town ($n=5$) before the follow-up measurements were excluded from the study. Of the remaining 1378 eligible individuals, 805 subjects (58%) took part in the follow-up home BP measurements.

In addition, 60 subjects were excluded for the following reasons: those who took <3 home BP measurements at follow-up ($n=20$) and those who had extreme levels of energy intake (in the upper or lower 2.5% of the range for all subjects: $n=40$). Finally, data from 745 subjects who were normotensive on baseline home BP (274 men and 471 women) were analysed. Compared with those who were ultimately excluded based on the exclusion criteria of the 1378 eligible individuals, the 745 participants who completely fulfilled the study criteria were more likely to be men, and of older age.

Home BP measurement

Baseline home BP was measured using the HEM701C monitor (Omron Healthcare Co., Ltd, Kyoto, Japan), a semiautomatic device based on the cuff-oscillometric method, which generates a digital display of both systolic BP and diastolic BP. We used HEM747ICN devices (Omron) for follow-up measurements. Both devices have been validated[28] and satisfy the criteria of the Association for the Advancement of Medical Instrumentation (the HEM747ICN is exactly same as the Omron HEM735C except that the latter does not incorporate an integrated circuit memory). As the circumference of the arm was <34 cm in most cases, we used a standard arm cuff in all cases.[27] In this study, home BP was defined as the mean of all first measurements recorded during the 4-week period. The mean ($\pm$ s.d.) number of home BP measurements was 23 ± 6. Hypertension was defined as use of antihypertensive medication and/or home BP values of $\geqslant 135/85$ mm Hg at follow-up measurement.[20–24]

Food frequency questionnaire

Standardized methodology was used to calculate fruit and vegetable intake from data obtained in a Japanese version of a food frequency questionnaire. The reproducibility and validity of this questionnaire were previously reported in detail.[29,30] The questionnaire asked about the average frequency of intake of each food during the previous year according to nine frequency categories ranging from no consumption to $\geqslant 7$ times per day. A standard portion size of one serving was specified for each food, and respondents were asked whether their usual portion was larger (>1.5 times), the same or smaller (<0.5) than the standard. In this study, we took into account energy from food sources of alcohol; for example, seasonings that include alcohol. However, we did not consider alcohol derived from alcoholic drinks such as beer and wine in the total energy count because we treated such alcohol intake as a separate variable. Nutritional supplements were not taken into account because there were few supplement users.

All food and nutrient intakes were adjusted for total energy intake using the residual method,[31–33] and separate regression models were performed to obtain the residuals for men and women. Following this procedure, subjects were divided into quartiles according to the intake of fruit and vegetables. In this study, the lowest quartiles were used as reference categories.

Statistical analysis

To examine how the intake of fruit or vegetables was associated with the risk of future home hypertension defined on the basis of home BP measurement, we used multiple logistic regression analyses after adjustment for other putative confounding factors

related to hypertension. These were gender (men/women), age (continuous), body mass index (BMI; $<25/\geqslant 25\,kg\,m^{-2}$), frequency of exercise (rarely or never, 1 or 2 h per week and >3 h per week), smoking status (never, past or current smoker), alcohol consumption (rarely or never, <540 ml of sake per day and ⩾540 ml of sake per day: 540 ml of sake = 81 g of alcohol), energy-adjusted fat intake and sodium intake (continuous), baseline systolic home BP (continuous) and a history of diabetes, hypercholesterolaemia and CVD (yes/no).

Moreover, we stratified the analysis by lifestyle factors, such as overweight ($BMI = 25\,kg/m^{-2}$ as cutoff), frequency of exercise, smoking status and alcohol consumption, to explore associations related to these factors. We tested interactions by introducing a multiplicative term into the main effect models. We also examined the combined effects of risk factors and fruit or vegetable intakes. For all analyses, statistical significance was defined as a two-tailed *P*-value of <0.05. All analyses were conducted using SPSS software version 14 for Windows (SPSS Inc., Chicago, IL, USA).

Results

At the time of the follow-up measurements, 222 subjects (29.8%) had developed home hypertension (mean duration of follow-up: 4.1 years). Among these, 70 were defined as having home hypertension because they had started treatment with antihypertensive medication.

The distributions of characteristics across quartile of each fruit and vegetable intake at baseline are shown in Table 1. In the study, the most commonly consumed type of fruit was citrus fruit ($18.5\,g\,day^{-1}$), followed by apple ($8.6\,g\,day^{-1}$), grape ($5.9\,g\,day^{-1}$) and watermelon ($5.6\,g\,day^{-1}$). Compared with those in the highest quartile of fruit intake, those in the lowest quartile were more likely to be men, of younger age, current smokers, heavier drinkers and with lower diastolic home BP. Subjects with the highest quartile of fruit intake tended to consume less energy and carbohydrate and more sodium, and fruit- and vegetable-related nutrients (that is, potassium, magnesium, β-carotene, folate, vitamin C and total dietary fibre) than subjects in the lowest quartile. As for food intake, the highest intake of fruit was associated with low intakes of rice, bread and noodles, and with high intakes of vegetables and seaweeds. Compared with those with highest quartile of fruit intake, subjects with quartile 3 of fruit intake reported more fat and less protein and calcium intake (table not shown, intake in quartile 3; fat, 42.7 ± 0.8 g; protein, 61.6 ± 0.6 g; and calcium 630 ± 14 mg). We observed similar tendencies for vegetable intake. In each category, the frequency of exercise and incidence of home hypertension at follow-up did not differ.

Table 2 shows the association between fruit and vegetable intake and the risk of future home hypertension. In the sex- and BMI-adjusted analysis, the highest quartile of fruit intake was associated with a significantly lower risk for future home hypertension (odds ratio compared with the lowest quartile for fruit intake: 0.44; $P=0.005$), whereas no association was observed for vegetable intake. After adjustment for putative confounding factors, these associations did not change. Compared with the lowest quartile for intake of fruit, a 60.0% lower risk of hypertension was found in those with the highest quartile of fruit intake ($P=0.004$). Further adjustment for putative confounding factors, vegetables and related nutrients (potassium, β-carotene, folate, vitamin C and total fibre) attenuated these results, but there was still a significantly lower risk of future home hypertension in the highest quartile of fruit intake (odds ratio = 0.45; $P=0.025$).

Regarding joint classification of quartiles of fruit intake and risk factors for home hypertension, Figure 1 shows the risk associated with BMI status at each quartile of fruit intake. The odds ratio for the comparison of overweight with highest quartile of fruit intake to overweight with lowest quartile of fruit intake was 0.21 ($P=0.005$). There was no significant interaction between BMI and fruit intake ($P>0.10$). When we adjusted for baseline diastolic home BP instead of systolic home BP, the results were almost the same.

Discussion

This study indicated that high fruit intake is strongly associated with a lower risk of future home hypertension. The inverse association between fruit intake and future home hypertension was persistent among subgroups of overweight and normal-weight individuals.

Our study has several strengths. It is the first to examine whether fruit and vegetable intake predicts hypertension measured by home BP. Measuring BP at home can eliminate several biases, such as the white-coat effect,[20–22] and therefore the results might more accurately determine the relationship between BP and fruit and vegetable intake. Because of the prospective design and exclusion of hypertensive subjects at baseline, we believe we could minimize the number of subjects who changed their diet because of a diagnosis of high BP.

The second strength is that, to the best of our knowledge, this is the first study to clarify the association between fruit and vegetable intake and future hypertension in Asian subjects.

Fruit/vegetable intake and future home hypertension

We found that high fruit intake was linked to a lower risk of future home hypertension, whereas no association was observed for high vegetable intake.

Table 1 Distribution of characteristics across quartiles of fruit and vegetable intake ($n = 745$)

	Quartile of fruit consumption		P-*value*	*Quartile of vegetable consumption*		P-*value*
	1 (n = 187)	*4 (n = 186)*		*1 (n = 187)*	*4 (n = 186)*	
Baseline						
Gender (men %)	51.3	26.9	<0.0001	62.6	18.3	<0.0001
Age	55.3 ± 0.8	57.4 ± 0.8	0.057	54.2 ± 0.8	59.0 ± 0.8[a]	<0.0001
Alcohol consumption (%)			0.010			<0.0001
Rarely or never	65.8	82.3		68.4	83.3	
<540 ml of sake per day	28.3	16.1		27.3	15.1	
⩾540 ml of sake per day	5.9	1.6		4.3	1.6	
Current smokers (%)	27.8	13.4	0.001	27.8	9.1	<0.0001
Exercise (rarely or never %)	76.5	83.3	0.290	79.7	80.1	0.643
Body mass index (kg m^{-2}, ⩾25%)	21.9	24.2	0.925	20.9	28.0	0.214
Home BP (mm Hg)						
Systolic	115.8 ± 0.7	113.6 ± 0.8	0.273	115.8 ± 0.7	114.3 ± 0.8	0.403
Diastolic	73.2 ± 0.5	71.3 ± 0.5	0.014	73.6 ± 0.5	71.2 ± 0.5[a]	0.002
Mean intakes of food and nutrients[b]						
Rice, bread and noodles (g)	566 ± 5	479 ± 5[a]	<0.0001	685 ± 15	397 ± 10[a]	<0.0001
Sugar (g)	6.6 ± 0.4	8.9 ± 0.4	<0.0001	4.3 ± 0.3	11.7 ± 0.6[a]	<0.0001
Nuts (g)	101.7 ± 4.7	73.6 ± 4.7	0.057	80.7 ± 7.5	100.2 ± 4.5[a]	0.021
Pulses (g)	2.7 ± 0.5	5.0 ± 0.5[a]	0.008	2.3 ± 0.3	4.7 ± 0.6[a]	0.001
Vegetables (g)	198.8 ± 8.4	249.2 ± 8.3[a]	<0.0001	90.3 ± 3.7	390.9 ± 8.6[a]	<0.0001
Seaweeds (g)	18.2 ± 1.1	22.8 ± 1.1[a]	0.009	13.4 ± 1.2	29.2 ± 1.4[a]	<0.0001
Fish and shellfish (g)	65.1 ± 3.1	58.5 ± 3.1	0.143	47.2 ± 4	68.6 ± 2.6[a]	<0.0001
Meats (g)	20.5 ± 1	17.2 ± 1.0	0.052	13.9 ± 0.9	22.7 ± 1.5[a]	<0.0001
Eggs (g)	29.5 ± 1.2	27.8 ± 1.2	0.744	22.6 ± 1.2	31.1 ± 1.5[a]	<0.0001
Dairy products (g)	220 ± 13	238 ± 13	0.497	241 ± 17	212 ± 12	0.166
Energy (kcal)	2163 ± 42	1952 ± 41	<0.0001	2135 ± 38	1897 ± 51[a]	<0.0001
Protein (g)	64.1 ± 0.6	62.3 ± 0.6	0.029	56.7 ± 1	68.2 ± 0.9[a]	<0.0001
Fat (g)	38.8 ± 0.9	40.1 ± 0.8	0.009	34.0 ± 0.9	45.3 ± 0.9[a]	<0.0001
Carbohydrates (g)	299.4 ± 0.7	305.9 ± 0.7[a]	<0.0001	336.8 ± 3.8	278.7 ± 2.8[a]	<0.0001
Sodium (mg)	4264 ± 151	5181 ± 150[a]	<0.0001	2959 ± 131	6610 ± 191[a]	<0.0001
Potassium (mg)	2396 ± 40	2797 ± 40[a]	<0.0001	1879 ± 23	3346 ± 48[a]	<0.0001
Calcium (mg)	631 ± 14	661 ± 14	0.332	549 ± 20	747 ± 17[a]	<0.0001
Magnesium (mg)	287 ± 1.5	313.7 ± 4.5[a]	0.001	232.8 ± 5.2	370 ± 5.2[a]	<0.0001
β-carotene (μg)	2806 ± 138	3686 ± 137[a]	<0.0001	1477 ± 56	5211 ± 202[a]	<0.0001
Folate (μg)	299.5 ± 8.5	335.3 ± 8.5[a]	0.026	205.4 ± 6.7	443.3 ± 10.7[a]	<0.0001
Vitamin C (mg)	59.9 ± 2.3	97.7 ± 2.3[a]	<0.0001	44.2 ± 1.7	111.4 ± 3.0[a]	<0.0001
Total dietary fibre (g)	14.8 ± 0.4	17.7 ± 0.4[a]	<0.0001	10.3 ± 0.3	23.1 ± 0.5[a]	<0.0001
Follow-up[c]						
Antihypertensive medication (%)	9.1	7.0	0.250	4.3	11.3	0.037
Home BP (mm Hg)						
Systolic	126.4 ± 1.1	123.9 ± 1.1	0.212	124.8 ± 1.1	124.4 ± 1.1	0.835
Diastolic	75.5 ± 0.7	73.4 ± 0.6	0.056	74.9 ± 0.7	72.8 ± 0.6	0.127
Home hypertension (%)[d]	34.8	24.2	0.076	31.6	26.9	0.450

Continuous variables are presented as mean ± s.e.
One-way analysis of variance (ANOVA) was used for continuous variables and χ^2 test for categorical variables, comparing quartiles of each food group.
[a]Statistical significance was defined as $P<0.05$ compared with quartile 1 (lowest) using Bonferroni *post hoc* test.
[b]Data were adjusted for total energy by the residual method.
[c]Mean duration of the period between the baseline and the follow-up home blood pressure (home BP) was 4.1 ± 0.7.
[d]Home hypertension was defined as use of antihypertensive medication and/or home BP values of ⩾135/85 mm Hg at follow-up.

Results of some studies, which examined the association between combined fruit and vegetable intake and risk of hypertension, are partially consistent with the present findings,[4–6,34] but no studies have shown significant inverse associations between intake of fruit alone and the risk of hypertension. Other studies have reported a significant protective association between intake of fruit and risk of CVD.[15,16] Our results are consistent with this.

Other related nutrients and home hypertension

We also analysed the intakes of potassium, folate, magnesium, vitamin C and β-carotene, which are highly correlated with fruit and vegetable intake. However, these dietary factors were not associated with the risk of home hypertension. Moreover, adjustment for these dietary factors did not significantly modify the findings. In this study, the most commonly consumed type of fruit was citrus fruit, followed by apple, grape and watermelon. Although

Table 2 Adjusted odds ratio (95% confidence interval) for the association between fruit and vegetable intake and the risk of future home hypertension ($n = 745$)

	Quartile 1	*Quartile 2*	*Quartile 3*	*Quartile 4*	P *for trend*
Fruit (g day^{-1})[a]	⩽38.40	38.41–63.80	63.8–100.02	100.03⩽	
Adjusted[b]	1.00	0.74 (0.44–1.26)	0.85 (0.80–1.44)	0.44 (0.25–0.78)	0.033
Adjusted[c]	1.00	0.64 (0.36–1.15)	0.70 (0.39–1.26)	0.40 (0.21–0.74)	0.037
Vegetables (g day^{-1})[a]	⩽143.41	143.42–211.55	211.56–282.75	282.76⩽	
Adjusted[b]	1.00	0.90 (0.52–1.57)	1.28 (0.74–2.23)	0.71 (0.40–1.24)	0.168
Adjusted[c]	1.00	0.96 (0.52–1.75)	1.11 (0.60–2.05)	0.75 (0.40–1.38)	0.597

[a]Data were adjusted for total energy by the residual method.
[b]Adjusted for age, gender and body mass index (BMI).
[c]Adjusted for age, gender, BMI, frequency of exercise, smoking status, alcohol consumption, energy-adjusted fat and sodium consumption, baseline systolic home BP, and a past history of diabetes, hypercholesterolaemia and cardiovascular disease.

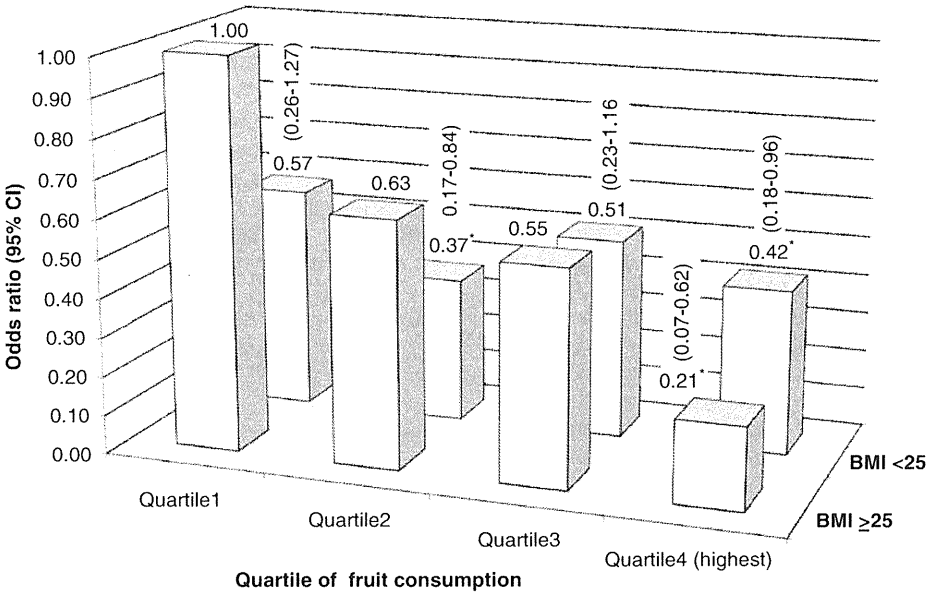

Figure 1 Multivariate odds ratio of home hypertension according to joint classifications of fruit intake and body mass index (BMI). The category of lowest fruit intake and the overweight (BMI of ⩾25) was used as reference. Model adjusted for age, gender, frequency of exercise, smoking status, alcohol consumption, energy-adjusted fat and sodium consumption, baseline systolic home BP and a past history of diabetes, hypercholesterolaemia and cardiovascular disease. *$P<0.05$.

individual dietary factors, such as vitamin C and folate, were not associated with risk of home hypertension, it is possible that the total balance of these factors in these commonly consumed fruits might be useful for the prevention of future hypertension.

Characteristics of fruit intake

These result, however, showed a lack of continuity in terms of risk of hypertension for each quartile of fruit intake, despite the significant association between the highest quartile of fruit intake and a lower risk of hypertension. Subjects in the third quartile of fruit intake reported higher fat and lower protein intake than those in the highest quartile, and thus the risk of hypertension might be influenced by these factors.

We also found no association between the highest quartile intake of vegetables and risk of hypertension. This study confirmed the findings of our previous cross-sectional study,[17] in that those who consumed more fruit and vegetables had higher sodium and fat intake. This might be attributable to seasonings, including soy sauce and table salt, and methods of cooking vegetables, such as deep frying. The higher fat and sodium intake among those who consumed more fruit might be attributable to the close correlation between the intake of fruit and vegetables. A number of factors, such as lifestyle, food availability, food culture and dietary habits, might also be related to BP and risk of hypertension.

In this study, we found significant differences in dietary characteristics across quartiles of fruit intake after adjusting for all putative confounding factors. Compared with subjects with higher intake of fruit,

those with the lowest intake of fruit consumed more carbohydrate-containing foods and meat, and less vegetables and seaweed. It therefore seems that a higher intake of fruit was associated with a healthier diet. As people consume diets consisting of a variety of foods with complex combinations of nutrients, the examination of only single foods could result in the identification of erroneous associations between dietary factors and disease. Furthermore, the risk of hypertension could be attributable to other food groups. When several nutrients with small BP-lowering effects are consumed together, the cumulative effects may be sufficient for detection. The dietary pattern approach using factor and cluster analyses[35] could provide more information regarding risk of home hypertension in further studies.

Study limitations

Several limitations of this study need to be discussed. First, information regarding food and nutrient intake in this study was obtained on the basis of dietary recall. The correlation between the food frequency questionnaire and usual diet has been well established, but there are several problems, for example, limited number of items and minimal information about portion size.

Second, we did not find a significant interaction between fruit consumption and BMI. However, a gradient declining risk of home hypertension with increasing fruit intake was apparent only for the overweight subjects, suggesting that such an interaction may have been present. Therefore, it is possible that the lack of statistical significance was because of the small size of the eight subgroups. Larger studies would be needed to clarify the presence of a statistically significant interaction between fruit consumption and BMI.

The possibility of selection bias also needs to be considered when generalizing the present findings, because only 54.1% of those eligible to participate in the study agreed to take part. As we excluded those who had home hypertension at baseline, this could mean that healthy people were more likely to be followed up. However, although the nonparticipants were older and had higher energy intake than those who participated in the study, other lifestyle factors did not differ significantly between participants and nonparticipants. Marked differences also exist in the epidemiology of home hypertension between Japan and Western countries;[36] thus, further research in other ethnic and cultural populations is needed to confirm the generalizability of our findings.

In this study, a higher intake of fruit was associated with a healthier lifestyle such as limited alcohol intake and avoidance of smoking. Therefore, although we adjusted for these confounding factors, it is possible that other factors associated with healthier lifestyle not measured in this study might confound the findings. Further studies with more detailed information on lifestyle-associated factors are required to further investigate the association observed in this study.

Conclusions

The present results from the Ohasama study suggest that high intake of fruit is potentially associated with a lower risk of future home hypertension. Although the mechanism for BP lowering through fruit and vegetable intake remains unclear,[37,38] selective intake of healthy foods and nutrients may prevent hypertension. Using home BP in general subjects enable to be considered highly health consciousness and subsequent early dietary intervention is expected to prevent hypertension and CVD.

What is known about this topic

- Fruit and vegetable intake has a powerful association with lower blood pressure and was found to reduce the risk of hypertension.
- But there are geographical differences in the types of food intake and risk factors among countries, and the relationship of diet with blood pressure in Asian populations has not been fully investigated.
- Furthermore, there is no study to examine the association between fruit and vegetable intake and the risk of future home hypertension determined by home blood pressure measurement.

What this study adds

- Higher intake of fruit is associated with a lower risk of future home hypertension.
- Higher intake of fruit is also associated with a healthier diet.

Conflict of interest

The authors declare no conflict of interest.

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