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Dietary Intake of Calcium in Relation to Mortality From Cardiovascular Disease

The JACC Study

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Background and Purpose—No prospective studies have examined the association between calcium intake and the risk of cardiovascular disease in Japanese populations with a low mean calcium intake.

Methods—Between 1988 and 1990, 110 792 Japanese subjects (46 465 men and 64 327 women) 40 to 79 years of age without a history of stroke, coronary heart disease, or cancer, completed a lifestyle questionnaire including food intake frequency under the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk Sponsored by Monbusho. By the end of 1999, after 515 029 person years of follow-up, 566 deaths from stroke (101 subarachnoid hemorrhages, 140 intraparenchymal hemorrhages, and 273 ischemic strokes) and 234 deaths from coronary heart disease had been documented.

Results—The intake of total calcium tended to be inversely associated with mortality from total stroke but not from coronary heart disease or total cardiovascular disease for men and women. The inverse association with dairy calcium intake was apparent for total stroke, both hemorrhagic and ischemic. The multivariate relative risk for men with highest versus lowest quintiles of dairy calcium intake was 0.53 (95% CI, 0.34 to 0.81) for total stroke, 0.46 (0.23 to 0.91) for hemorrhagic stroke, and 0.53 (0.29 to 0.99) for ischemic stroke; corresponding relative risks for women were 0.57 (0.38 to 0.86), 0.51 (0.28 to 0.94), and 0.50 (0.27 to 0.95).

Conclusions—Dietary calcium intake from dairy products was associated with reduced mortality from stroke for Japanese men and women. **(*Stroke*. 2006;37:20-26.)**

Key Words: calcium ■ follow-up studies ■ mortality ■ stroke

Findings from studies assessing the relationship between dietary intake of milk, dairy products, and calcium with the risk of cardiovascular disease have been inconsistent. Five prospective studies have examined the association between milk or calcium intake with the risk of mortality or incidence of coronary heart disease; however, none of these studies demonstrated any significant association.[1–5] Two prospective studies have shown that dietary intake of milk or calcium reduces the risk of ischemic stroke;[1,2] however, 2 other studies failed to demonstrate this association.[3,4] These studies were undertaken in Western countries where the intake of calcium is greater than that in Eastern countries.

The mean calcium intake among the Japanese is far lower than that of whites in Western countries, largely because of a lower intake of milk and dairy products.[6,7] According to the national nutrition surveys, the mean intake of calcium in Japan was 559 mg per day for men and 535 mg per day for women in 2002,[6] whereas corresponding values in United States were 966 mg per day and 765 mg per day between 1999 and 2000.[7] The purpose of the present study was to

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TABLE 1. Baseline Characteristics and Risk Factors According to Quintile of Total Calcium Intake

	Quintiles of Calcium Intake (mg per day)									
	Men					Women				
	1 (low)	2	3	4	5 (high)	1 (low)	2	3	4	5 (high)
Total calcium										
No. of subjects	4623	4624	4623	4624	4623	7121	7122	7122	7122	7122
Median calcium intake, mg/d	250	363	449	536	665	266	379	462	545	667
Mean age, y	55	56	56	57	57	56	56	56	56	56
Mean body mass index, kg/m^2	22.6	22.7	22.7	22.7	22.8	23.0	23.0	22.9	22.8	22.9
Current smokers, %	58	56	52	52	51	8	5	4	4	4
Mean ethanol intake, g/d	35	34	34	33	33	13	11	10	9	9
History of hypertension, %	20	20	19	17	14	22	21	20	19	16
History of diabetes, %	6	6	6	6	5	3	4	3	3	3
Mean energy intake, kcal/d	1349	1520	1628	1740	1997	1074	1219	1312	1411	1627
Mean potassium intake, mg/d	1216	1628	1919	2213	2763	1317	1729	1999	2273	2773
Dairy calcium										
No. of subjects	3985	4386	3747	4769	4181	6544	6704	8128	4240	6703
Median calcium intake, mg/d	0	26	61	121	150	0	32	121	127	173
Mean age, y	58	57	54	54	57	58	55	57	55	56
Mean body mass index, kg/m^2	22.5	22.7	22.7	22.6	22.7	23.0	22.9	22.8	22.8	22.7
Current smokers, %	62	58	53	52	44	7	6	4	3	4
Mean alcohol intake, g/d	38	35	34	33	31	13	11	11	9	9
History of hypertension, %	18	18	17	18	17	19	20	19	19	18
History of diabetes, %	5	4	5	7	7	2	3	4	4	4
Mean energy intake, kcal/d	1586	1593	1675	1652	1723	1239	1283	1335	1349	1439
Mean potassium intake, mg/d	1667	1738	1974	2043	2290	1694	1861	2043	2139	2374
Nondairy calcium										
No. of subjects	4213	4214	4214	4214	4213	6463	6464	6464	6464	6464
Median calcium intake, mg/d	211	302	369	440	550	221	306	369	434	532
Mean age, y	58	55	56	56	56	56	56	56	56	56
Mean body mass index, kg/m^2	22.6	22.6	22.7	22.7	22.7	22.9	22.8	22.8	22.8	22.9
Current smokers, %	55	54	52	54	55	7	5	4	4	4
Mean alcohol intake, g/d	34	34	34	34	35	12	11	10	10	9
History of hypertension, %	21	19	18	17	13	22	20	19	19	15
History of diabetes, %	7	6	6	5	4	4	4	3	3	2
Mean energy intake, kcal/d	1321	1495	1624	1752	2036	1053	1208	1309	1422	1649
Mean potassium intake, mg/d	1192	1613	1909	2232	2780	1291	1717	1993	2283	2796

determine the relationship between calcium intake and mortality from cardiovascular disease in a large prospective study of Japanese men and women.

Methods

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sport, and Science, was conducted from 1988 to 1990. A total of 110 792 subjects (46 465 men and 64 327 women) 40 to 79 years of age completed self-administered questionnaires about their lifestyles and medical histories of previous cardiovascular disease and cancer. They were enrolled from 45 communities across Japan, mostly when they underwent municipal health screening examinations according to the Health Law for the Aged.[8,9] The sampling methods and protocols of the JACC Study have been described previously.[8] Subjects with a previous history of stroke, coronary heart disease, or cancer were excluded from analysis. Therefore, 41 782 men and 52 901 women were followed; 21 068 men and 32 319 women provided valid responses to questions regarding milk, cheese, and yogurt consumption and were enrolled in the present study.

Mortality Surveillance

For mortality surveillance in each community, investigators conducted a systematic review of death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of death coded according to the International Classification of Disease, 9th Revision from 1988 to 1994, and 10th Revision from 1995 to 1999, for the National Vital Statistics. In Japan, registration of death is required by the Family Registration Law and is believed to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by

TABLE 2. Multivariate Relative Risks (95% CI) of Mortality From Stroke, Coronary Heart Disease, and Total Cardiovascular Disease According to Quintile of Total Calcium Intake

	Men					
	1 (low)	2	3	4	5 (high)	*P* for Trend
Person years	43 685	43 951	44 300	44 674	44 514	
Total stroke						
n	61	76	69	59	57	
Age-adjusted RR	1.0	1.14 (0.81–1.59)	0.97 (0.69–1.37)	0.81 (0.56–1.15)	0.77 (0.53–1.10)	0.09
Multivariate RR*	1.0	1.14 (0.76–1.70)	0.90 (0.56–1.45)	0.69 (0.40–1.18)	0.68 (0.37–1.26)	0.13
Hemorrhagic stroke						
n	31	32	23	16	19	
Age-adjusted RR	1.0	0.97 (0.59–1.58)	0.67 (0.39–1.15)	0.45 (0.25–0.83)	0.53 (0.30–0.94)	0.05
Multivariate RR*	1.0	0.94 (0.52–1.70)	0.60 (0.29–1.26)	0.39 (0.17–0.93)	0.59 (0.22–1.58)	0.12
Intraparenchymal hemorrhage						
n	23	20	13	10	14	
Age-adjusted RR	1.0	0.81 (0.44–1.47)	0.50 (0.25–0.99)	0.37 (0.18–0.79)	0.52 (0.27–1.00)	0.21
Multivariate RR*	1.0	0.86 (0.42–1.76)	0.51 (0.20–1.29)	0.38 (0.13–1.13)	0.78 (0.24–2.58)	0.20
Subarachnoid hemorrhage						
n	8	12	10	6	5	
Age-adjusted RR	1.0	1.44 (0.59–3.52)	1.17 (0.46–2.97)	0.68 (0.24–1.98)	0.57 (0.19–1.73)	0.23
Multivariate RR*	1.0	1.15 (0.40–3.30)	0.80 (0.23–2.78)	0.41 (0.09–1.78)	0.34 (0.06–1.92)	0.30
Ischemic stroke						
n	28	37	40	32	35	
Age-adjusted RR	1.0	1.19 (0.73–1.95)	1.17 (0.72–1.90)	0.93 (0.56–1.55)	1.00 (0.61–1.64)	0.68
Multivariate RR*	1.0	1.20 (0.67–2.14)	1.11 (0.57–2.17)	0.74 (0.35–1.59)	0.71 (0.30–1.67)	0.32
Coronary heart disease						
n	37	26	33	32	20	
Age-adjusted RR	1.0	0.64 (0.39–1.06)	0.77 (0.48–1.24)	0.72 (0.45–1.16)	0.44 (0.26–0.76)	0.23
Multivariate RR*	1.0	0.84 (0.47–1.50)	1.20 (0.62–2.30)	1.27 (0.60–2.68)	0.92 (0.37–2.29)	0.43
Total cardiovascular disease						
n	140	141	135	135	134	
Age-adjusted RR	1.0	0.92 (0.73–1.16)	0.83 (0.66–1.05)	0.81 (0.64–1.02)	0.78 (0.62–0.99)	0.56
Multivariate RR*	1.0	0.98 (0.75–1.30)	0.93 (0.67–1.29)	0.92 (0.64–1.32)	0.97 (0.64–1.48)	0.95

*Further adjusted for body mass index (kg/m^2), history of hypertension (yes or no), history of diabetes (yes or no), smoking status (4 categories), ethanol intake (6 categories), potassium intake (quintile), and total energy (quintile).

RR indicates relative risk.

death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case. The follow-up was conducted at the end of 1999. The average follow-up period for the participants was 9.6 years. The present study was approved by the ethics committees of the Nagoya University School of Medicine and the University of Tsukuba.

Intake of Milk, Yogurt, and Cheese and Calculation of Calcium Intake

Each participant was asked to record the frequency of the intake of 35 foods including milk, yogurt, and cheese. Five responses were possible for each food item: "rarely," "1 to 2 days per month," "1 to 2 days per week," "3 to 4 days per week," and "almost every day"; the consumption of each food was calculated by multiplying the frequency score of consumption of each food 0, 0.38, 1.5, 3.5, and 7, respectively. Each portion size was estimated from the validation study conducted in 85 individuals from the baseline participants. For example, 121 mg of calcium for 1 serving of milk, 118 mg for 1 serving of yogurt, and 107 mg for 1 serving of cheese. Based on Japan Food Table version 4, the average daily intake of nutrients and total energy was calculated by multiplying the frequency of consumption of each item by its nutrient content and energy per serving and totaling the nutrient intake for all food items.[10]

We obtained the nutritional data of valid calcium intake for 23 117 men and 35 609 women. The reproducibility and validity of this dietary questionnaire was reported previously.[10] Briefly, the Spearman rank correlation coefficients between first and second questionnaires, conducted 1 year apart, were 0.76 in total calcium intake, 0.53 in dairy calcium intake, and 0.76 in nondairy calcium intake. The coefficients between the average of 2 questionnaires and 4 3-day dietary records were 0.44 in total calcium intake, 0.58 in dairy calcium intake, and 0.17 in nondairy calcium intake.

Statistical Analysis

Statistical analysis was based on sex-specific mortality rates of stroke during the follow-up period from 1989 to 1999. For each participant, the person years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving out of the community, or the end of 1999, whichever was first. The

TABLE 2. (Continued)

Women					
1 (low)	2	3	4	5 (high)	*P* for Trend
68 759	69 197	69 276	69 975	70 277	
70	82	73	42	55	
1.0	1.27 (0.92–1.75)	1.16 (0.84–1.61)	0.67 (0.46–0.99)	0.92 (0.65–1.32)	<0.01
1.0	1.38 (0.95–2.01)	1.24 (0.79–1.95)	0.69 (0.40–1.18)	0.94 (0.51–1.72)	0.01
24	39	35	21	24	
1.0	1.69 (1.02–2.81)	1.53 (0.91–2.57)	0.92 (0.51–1.65)	1.08 (0.61–1.90)	0.08
1.0	2.14 (1.19–3.85)	1.93 (0.96–3.88)	1.04 (0.46–2.37)	1.03 (0.41–2.59)	0.09
15	19	14	9	14	
1.0	1.34 (0.68–2.64)	1.00 (0.48–2.08)	0.65 (0.28–1.48)	1.04 (0.50–2.16)	0.35
1.0	1.95 (0.90–4.24)	1.80 (0.68–4.74)	1.18 (0.36–3.87)	1.52 (0.41–5.70)	0.78
9	20	21	12	10	
1.0	2.28 (1.04–5.01)	2.41 (1.10–5.26)	1.37 (0.58–3.26)	1.17 (0.47–2.87)	0.14
1.0	2.53 (1.03–6.24)	2.19 (0.78–6.20)	1.06 (0.33–3.44)	0.80 (0.21–3.06)	0.08
38	38	28	16	23	
1.0	1.14 (0.72–1.78)	0.89 (0.55–1.46)	0.52 (0.29–0.93)	0.80 (0.48–1.34)	0.06
1.0	0.97 (0.57–1.66)	0.73 (0.38–1.41)	0.41 (0.18–0.91)	0.80 (0.33–1.95)	0.07
38	21	25	17	15	
1.0	0.60 (0.35–1.03)	0.74 (0.45–1.22)	0.51 (0.29–0.90)	0.48 (0.26–0.87)	0.51
1.0	0.88 (0.48–1.62)	1.28 (0.62–2.61)	0.84 (0.35–2.02)	0.87 (0.31–2.45)	0.50
153	156	136	98	101	
1.0	1.11 (0.89–1.39)	1.00 (0.80–1.27)	0.73 (0.57–0.94)	0.80 (0.62–1.02)	<0.01
1.0	1.29 (0.99–1.67)	1.24 (0.90–1.69)	0.92 (0.64–1.34)	1.14 (0.74–1.74)	0.14

sex-specific relative risk of mortality from stroke was defined as the death rate among participants according to the quintile of calcium intake: <315, 315 to 407, 408 to 490, 491 to 589, and ≥590 mg per day for total calcium, <7, 7 to 37, 38 to 120, 121 to 127, and ≥128 mg per day for dairy calcium, and <262, 262 to 335, 336 to 403, 404 to 484, and ≥485 mg per day for nondairy calcium, in men, and in women, <331, 331 to 421, 422 to 501, 502 to 595, and ≥596 mg per day for total calcium, <12, 12 to 64, 65 to 122, 123 to 143, and ≥144 mg per day for dairy calcium, and <269, 269 to 336, 337 to 399, 400 to 473, and ≥474 mg per day for nondairy calcium.

Age-adjusted means, proportions of selected cardiovascular risk factors, and the calcium intake were presented according to the quintile of calcium intake. Statistical testing was not conducted because of the large sample size. The age-adjusted and multivariate-adjusted relative risks and their 95% CIs were calculated after adjustment for age and potential confounding factors by using the Cox proportional hazard model. These confounding variables included body mass index (sex-specific quintiles), smoking status (never, ex-smokers, and current smokers of 1 to 19 and ≥20 cigarettes per day), alcohol intake category (never, ex-drinkers, and current drinkers of ethanol at 1 to 22, 23 to 45, 46 to 68, and ≥69 g per day), history of hypertension (yes or no), history of diabetes (yes or no), energy intake (sex-specific quintiles), and potassium intake (sex-specific quintiles). Test for a linear trend across the calcium intake quintiles were conducted by linear regression using a median variable of calcium intake in each calcium intake quintile.

The significance of the interactions of smoking status (yes or no) or alcohol status (yes or no) with dairy calcium intake (dummy variables for sex-specific quintiles) was tested using an interaction term of 2 variables in multivariate models.

Cause-specific mortality was calculated according to the International Classification of Disease, 9th and 10th revisions, which define total stroke (ICD-9 codes 430 to 438 and ICD-10 codes I60 to I69), and further subgroups total stroke into subarachnoid hemorrhage (ICD-9 code 430 and ICD-10 code I60), intraparenchymal hemorrhage (ICD-9 code 431 and ICD-10 code I61), and ischemic stroke (ICD-9 codes 433 to 434 and ICD-10 codes I63 and I693).

Results

Among 21 068 men and 32 319 women followed up for 9.6 years, there were 284 deaths from stroke (37 subarachnoid hemorrhage, 76 intraparenchymal hemorrhage, and 146 ischemic stroke) in men and 282 in women (n=64, 64, and 127, respectively).

TABLE 3. Multivariate Relative Risks (95% CI) of Mortality From Stroke, Coronary Heart Disease, and Total Cardiovascular Disease According to Quintile Group of Dairy Calcium Intake

	Men					
Dairy calcium	1 (low)	2	3	4	5 (high)	*P* for Trend
Person year	37 644	41 972	35 817	45 270	40 417	
Total stroke						
n	66	60	43	80	35	
Multivariate RR	1.0	1.05 (0.75–1.49)	0.88 (0.59–1.31)	1.00 (0.72–1.39)	0.53 (0.34–0.81)	<0.01
Hemorrhagic stroke						
n	33	25	20	23	12	
Multivariate RR	1.0	0.87 (0.52–1.45)	0.89 (0.50–1.58)	0.67 (0.39–1.15)	0.46 (0.23–0.91)	0.25
Intraparenchymal hemorrhage						
n	21	15	15	15	10	
Multivariate RR	1.0	0.83 (0.43–1.61)	1.11 (0.56–2.21)	0.71 (0.36–1.39)	0.63 (0.28–1.38)	0.51
Subarachnoid hemorrhage						
n	12	10	5	8	2	
Multivariate RR	1.0	0.90 (0.39–2.09)	0.55 (0.19–1.59)	0.59 (0.24–1.48)	0.19 (0.04–0.87)	0.25
Ischemic stroke						
n	27	34	21	46	18	
Multivariate RR	1.0	1.42 (0.87–2.33)	0.93 (0.51–1.68)	1.22 (0.76–1.97)	0.53 (0.29–0.99)	<0.01
Coronary heart disease						
n	29	28	26	31	21	
Multivariate RR	1.0	1.04 (0.62–1.73)	1.19 (0.69–2.05	0.94 (0.57–1.57)	0.80 (0.45–1.44)	0.63
Total cardiovascular disease						
n	136	119	98	158	96	
Multivariate RR	1.0	1.01 (0.79–1.29)	0.99 (0.76–1.30)	0.99 (0.78–1.25)	0.73 (0.55–0.95)	0.06

Further adjusted for body mass index (kg/m^2), history of hypertension (yes or no), history of diabetes (yes or no), smoking status (4 categories), ethanol intake (6 categories), potassium intake (quintile), and total energy (quintile).

RR indicates relative risk.

Table 1 shows sex-specific selected cardiovascular risk factors, total energy, and potassium intake according to quintiles of total, dairy, and nondairy calcium intake. Compared with men and women in the lowest quintile, those in the highest quintile smoked less, drank less, had higher intakes of total energy and potassium, and were less likely to have a history of hypertension.

Table 2 shows age-adjusted and multivariate relative risks (95% CI) of stroke, stroke subtypes, coronary heart disease, and cardiovascular disease according to quintiles of total calcium intake. For men and women, total calcium intake tended to be inversely associated with mortality from total and ischemic strokes: the associations were of statistical significance for total stroke in women and of borderline significance for ischemic stroke in women but did not reach statistical significance for either end point in men. When men and women were combined, adjusting for sex, the multivariate relative risk in the highest versus lowest quintiles of total calcium intake was 0.86 (0.56 to 1.31) for total stroke (*P* for trend=0.003) and 0.74 (0.41 to 1.36) for ischemic stroke (*P* for trend=0.03). Total calcium intake was not associated with mortality from coronary heart disease or total cardiovascular disease.

Table 3 shows multivariate relative risks according to quintiles of dairy calcium intake. For dairy calcium, there was an inverse association between dairy calcium intake and mortality from total stroke, either hemorrhagic or ischemic, and total cardiovascular disease but not coronary heart disease. The multivariate relative risk (95% CI) in the highest versus lowest quintiles of dairy calcium intake for men was 0.53 (0.34 to 0.81) for total stroke and 0.46 (0.23 to 0.91) for hemorrhagic stroke, 0.53 (0.29 to 0.99) for ischemic stroke, and 0.73 (0.55 to 0.95) for total cardiovascular disease. The respective relative risk for women was 0.57 (0.38 to 0.86), 0.51 (0.28 to 0.94), 0.50 (0.27 to 0.95), and 0.77 (0.58 to 1.03). These associations did not differ significantly when stratified by smoking and drinking status (data not shown in the table). For example, the multivariate relative risk of total stroke for men and women combined in the highest versus lowest quintiles of dairy calcium intake was 0.55 (0.32 to 0.94) among current smokers and 0.63 (0.44 to 0.92) among nonsmokers (*P* for interaction=0.31), 0.37 (0.23 to 0.59) among current drinkers, and 0.76 (0.52 to 1.11) among nondrinkers (*P* for interaction=0.84). There was no association between nondairy calcium intake and mortality from cardiovascular disease (data not shown in the table).

TABLE 3. (Continued)

Women					
1 (low)	2	3	4	5 (high)	*P* for Trend
63 217	65 046	78 849	41 463	65 330	
86	53	86	21	36	
1.0	0.83 (0.58–1.17)	0.95 (0.70–1.30)	0.59 (0.36–0.96)	0.57 (0.38–0.86)	0.04
39	21	43	8	17	
1.0	0.64 (0.38–1.10)	0.97 (0.62–1.52)	0.41 (0.19–0.89)	0.51 (0.28–0.94)	0.04
20	8	23	4	9	
1.0	0.52 (0.23–1.20)	1.18 (0.63–2.21)	0.50 (0.17–1.51)	0.65 (0.28–1.52)	0.11
19	13	20	4	8	
1.0	0.73 (0.36–1.49)	0.80 (0.42–1.53)	0.34 (0.11–1.02)	0.41 (0.17–0.97)	0.22
42	25	36	10	14	
1.0	0.88 (0.53–1.45)	0.88 (0.56–1.40)	0.68 (0.33–1.37)	0.50 (0.27–0.95)	0.31
21	26	31	9	12	
1.0	1.87 (1.04–3.34)	1.72 (0.97–3.05)	1.30 (0.58–2.91)	1.06 (0.50–2.25)	0.40
157	111	180	49	80	
1.0	0.98 (0.77–1.25)	1.16 (0.93–1.44)	0.79 (0.57–1.10)	0.77 (0.58–1.03)	0.01

Discussion

In this large prospective study of middle-aged Japanese men and women, we observed lower risks of mortality from total stroke, either hemorrhagic or ischemic, with increased intake of dairy calcium.

Two cohort studies have shown an inverse relationship between total calcium intake, specifically dairy calcium intake, and the risk of ischemic stroke.[1,2] The Honolulu Heart Program of 3150 men 55 to 68 years of age reported that the multivariate relative risk of thromboembolic stroke in a 22-year follow-up was 1.8 (1.1 to 2.9) for the lowest versus highest quintiles of total calcium intake and 1.5 (1.0 to 2.2) for those of dairy calcium intake.[1] The Nurses' Health Study of 85 764 women 34 to 59 years of age showed that the multivariate relative risk of ischemic stroke was 0.69 (0.50 to 0.95) for the highest versus lowest quintiles of total calcium intake.[2] A cohort study of 265 070 Japanese >40 years of age also showed lower mortality from cerebral hemorrhage and ischemic stroke for dairy milk intake ≥4× per week compared with less than once per week; the multivariate relative risk was 0.74 (0.68 to 0.80) and 0.85 (0.77 to 0.92), respectively.[11] However, this study did not examine the reproducibility or validity of dietary assessments, nor did it calculate calcium intake.

The mechanisms responsible for the inverse association between dairy calcium and risk of stroke merit some discussion. A well-designed clinical trial demonstrated that diets rich in low-fat milk and dairy products reduced blood pressure levels.[12] Calcium in milk and dairy products can be absorbed more efficiently than that in nondairy products because phosphorylated serine and threonine residues, abundant in milk and dairy products, make calcium ion soluble during digestion.[13] In addition, calcium has a hypotensive effect, particularly in individuals with a high sodium intake. Calcium also has antiplatelet aggregation effects.[14,15] In addition to these beneficial effects of calcium, whey peptides in milk and dairy products may have a hypotensive effect through inhibition of the angiotensin-converting enzyme.[16]

In the present study, calcium intake was not associated with mortality from coronary heart disease in either sex. Our finding is consistent with the results of previous studies that milk intake was not associated with mortality or incidence of coronary heart disease among middle-aged men.[3,4] However, a recent prospective study of postmenopausal women showed a 33% lower mortality of coronary heart disease associated with the highest quintile of calcium intake.[17]

Some limitations of the present study warrant discussion. First, there would be the residual confounding on the association between calcium intake and cardiovascular disease. For example, histories of hypertension and diabetes were self-reported. Thus, it is possible that we did not adjust for these confounding variables fully. Also, current smokers or drinkers had a lower calcium intake than nonsmokers or nondrink-

ers. However, we found similar inverse associations between calcium intake and mortality for smokers and nonsmokers and for drinkers and nondrinkers.

Second, we used only 3 foods, namely milk, yogurt, and cheese, not other dairy foods and calcium supplements. However, validation and reliability assessments showed that the validity and reliability of dairy calcium intake was very good (r=0.55; P<0.0001). During the baseline survey, we did not ask for information on calcium supplements in the questionnaire; however, the use of calcium supplements was not common in Japan in the 1990s.

In conclusion, the present study showed that calcium intake from milk and dairy products was associated with a reduced risk of mortality from total stroke, either hemorrhagic or ischemic, among Japanese men and women. Clinical trials are necessary to confirm this finding.

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D. 今後の計画

死亡者の追跡は、2年ごとに実施しており、既に平成15年度までの調査が完了している。来年度は平成16年及び17年の追跡を実施する予定である。

来年度は、ナトリウム・カリウム摂取と循環器死亡の関連、魚、野菜、果物、大豆摂取と循環器死亡との関連、高血圧治療者における血圧値と循環器死亡（いわゆるJカーブ現象）の関連、運動と喫煙の相互作用と循環器死亡の関連についての分析に着手し、これらについては来年度中に完了する予定である。

2．大迫コホート

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1)大迫コホートの概要

大迫（おおはさま）コホート研究は、24 時間自由行動下血圧および家庭における自己測定血圧（家庭血圧）を用いた世界初の住民ベースの疫学研究であるという特色を持ち、これまでの 10 年以上の追跡を通じ、「我が国発、世界初」のエビデンスを発信し続けてきた。

大迫研究の特色は、当時臨床で使用が開始されていたものの、その基準値・分布・随時血圧との差異、などの疫学的特性が未知であった 24 時間自由行動下血圧および家庭血圧の意義を、世界で初めて明らかにした点である。　1997 年米国合同委員会 JNC 勧告、1999 年 WHO/ISH 高血圧ガイドライン、ヨーロッパの 2003 年 ESH/ESC 高血圧ガイドラインをはじめとする国際的ガイドライン、またいくつかの諸外国のガイドラインにおいて、家庭血圧・自由行動下血圧の臨床的意義に関する記述の一部が大迫研究の成果を基として提示されたことは、本邦の疫学データが国際的ガイドラインの基盤となったという点で希有なことであった。

1．大迫町について

大迫町は盛岡の南 30km に位置し、果樹栽培を主体とした兼業農家で成り立つ、東北地方の典型的な一農村であり、行政的に内川目、外川目、亀ヶ森、大迫の 4 地区に分かれている。

大迫町の医療機関としては岩手県立大迫病院が多くの一次及び二次医療を担当し、三次医療は盛岡市、花巻市の医療機関が担当している。

本研究の開始時（1986 年）、大迫町の人口は約 9300 人であったが、若年者の流出、出生の減少、高齢者の死亡により、人口は約 7000 人に減少している。　平成 12 年国勢調査報告により、大迫町の人口は、男性 3318 名、女性 3619 名の計 6937 名であり、65 歳以上の高齢者人口割合は、29.8%である。

2. 研究内容

大迫町では、1988-1995年（第1期）、1997-2000年（第2期）、2001-2004年（第3期）、2005年-（第4期）の4期にわたり、家庭血圧測定を中心とした保健事業を実施している。

(1) 血圧測定

家庭血圧測定は8歳以上の全ての人口構成員を対象に、24時間自由行動下血圧は20歳以上の全ての人口構成員を対象に行った。それぞれ　第1期4236名、第2期2595名、第3期2381名が家庭血圧測定事業に、20歳以上の対象者中　第1期2035名が、24時間自由行動下血圧測定事業にそれぞれ同意し、測定を行った。事業開始前に、各地区の公民館において、医師・保健師による24時間自由行動下血圧、家庭血圧測定の意義と実際の測定のための講習会を開催した。各世帯から必ず一人以上の参加を求め、未参加世帯には、保健師の個別訪問による説明と指導を行った。その後各世帯に一台ずつ家庭用自動血圧計を配布した。家庭血圧は朝、起床後、1日1回、排尿後、朝食前に、座位で2分間の安静後に測定し、この一定の測定条件を遵守するよう指導を行い、毎年1ヶ月間の血圧値の記録及び提出を求めた。家庭血圧値または24時間自由行動下血圧の平均が135/80mmHgの者に対しては保健師が個別に生活・栄養指導を行い、必要に応じて医療機関受診を推奨した。以上の過程を通じ、1988年より現在にいたるまで同町民に家庭血圧測定を普及させてきた。

(2) 高齢者頭部MRI検診事業

家庭血圧測定事業に参加した55歳以上の住民に対し、頭部MRI撮影を施行した。　第1期446名、第2期638名、第3期552名が、頭部MRI測定事業にそれぞれ同意し、測定を行った。　また本事業参加者に対して、頚動脈超音波検査、脈波伝播速度、Augmentation Index, 指尖容積脈波、24時間ホルター心電図、認知機能検査（ミニメンタルテスト・反応時間）、および動脈硬化関連血液尿生化学パラメーター（クレアチニンクリアランス、尿中微量アルブミン、BNP、フィブリノーゲン、リポプロテイン(a)、血漿レニン活性、高感度CRP）、脈波伝播速度、等の測定も実施している。

(3) 糖尿病検診

近年の糖尿病増加を考慮に入れ、第2期より家庭血圧測定事業に参加した35歳以上の住民に対し、75g経口糖負荷試験（OGTT）による糖尿病検診を開始している。第2期592名、第3期307名が、これまで本事業に参加し測定を行っている。

(4) 生活習慣調査

第2期に35歳以上の全町民を対象に、生活習慣全般についての詳細なアンケート調査

を実施し、4268名より有効回答を得ている。

(5) 追跡調査

生命予後および脳卒中発症状況等に関する長期的な追跡調査を継続している。

3. 研究結果

以下がこれまでの主要な研究結果の概要である。

■ 家庭血圧を用いた追跡研究

1) 家庭血圧の脳心血管系死亡・脳卒中発症予測能は、測定回数によらず随時血圧よりすぐれている。

2) 家庭血圧 135/85mmHg 以上は高血圧である。

3) 家庭収縮期血圧は拡張期血圧よりも優れた脳心血管系死亡予測能を持つ。

4) 家庭脈拍数高値は脳心血管系死亡リスクである。

■ 24 時間自由行動下血圧を用いた追跡研究

1) 24 時間自由行動下血圧の脳心血管系死亡・脳卒中発症予測能は、随時血圧より優れている。

2) 24 時間自由行動下血圧 135/80mmHg 以上は高血圧である。

3) 夜間睡眠時に血圧が低下しないと脳心血管系死亡のリスクが高い。

4) 昼間血圧変動大・昼間脈拍変動小は脳心血管系死亡の高リスクである。

* 補足

大迫町は平成 18 年 1 月 1 日に花巻市と合併したが、本事業については、合併後の新花巻市においても「健康づくりフロンティア事業」として継続されている。

2)最新の研究成果

1.家庭血圧値および他の循環器疾患危険因子の相互作用に関する研究

別添論文

Kei Asayama, Takayoshi Ohkubo, Masahiro Kikuya, Hirohito Metoki, Taku Obara , Haruhisa Hoshi, Junichiro Hashimoto, Kazuhito Totsune, Hiroshi Satoh, Yutaka Imai. Use of 2003 European Society of Hypertension - European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study. *European Heart Journal* 2005;26:2026-31.

要約

本態性高血圧は脳心血管疾患の主要な危険因子であり、高血圧の発症予防・合併症進展の予防は極めて重要な課題である。一方、各国の高血圧管理ガイドラインが近年相次いで改定され、血圧値および他の危険因子の組み合わせによる重症度分類が提唱されているが、本邦における最適な高血圧診療の基礎情報となる本邦独自のエビデンス集積は質・量ともに不十分である。

本研究の目的は、家庭における自己測定血圧(家庭血圧)を用いて、米国の JNC-7 ガイドラインならびに 欧州の 2003 ESH-ESC ガイドラインで提唱された血圧および他の危険因子に基づいた高血圧重症度の分類法の、本邦一般住民における妥当性を検討することである。

40 才以上の大迫町民 1702 例の高血圧重症度を、JNC-7 および 2003 ESH-ESC のそれぞれに準拠して分類した。JNC-7 分類では、血圧値で Group 1 (正常血圧)、Group 2 (高血圧前症)、Group 3 (高血圧ステージ 1)、Group 4 (高血圧ステージ 2)の 4 グループに、更に加療積極適応の有無で Group 2 から 4 を a,b 各 2 群に、計 7 群に分類した。一方、2003 ESH-ESC 分類では、対象を血圧値で 6 段階にまず分類し、更に 2003 ESH-ESC ガイドラインで提唱されている他の合併症の有無・個数に応じた計 5 群 (正常リスク群、低リスク群、中等度リスク群、高リスク群、極めて高リスク群)のリスク分類に当てはめた。

平均 10.6 年の追跡の結果、153 例の初発脳卒中が観察され、両分類のいずれも本邦の一般集団に適切であることが判明したが、簡略化されたリスク分類を採用する JNC-7 分類よりも、包括的な 2003 ESH-ESC リスク分類が、また検診時随時血圧を用いた場合よりも一層有効であった。

本邦の一般地域住民の脳卒中発症予測には、JNC-7 分類、2003 ESH-ESC 分類のいずれも良好に適合するが、JNC-7 のような単純化された分類法よりも、2003 ESH-ESC に代表される包括的なリスク分類法が、本邦には一層適切であると考えられた。一方、いずれの分類法でも随時血圧より家庭血圧に基づいた場合に予後予測能が一段と高まり、家庭血圧の有用性が改めて示された。

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Use of 2003 European Society of Hypertension–European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study

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KEYWORDS
Blood pressure;
Home measurement;
Screening measurement;
Stroke;
ESH-ESC guidelines;
Risk stratification

Aims To evaluate the predictive power of the risk stratification system proposed in the 2003 European Society of Hypertension–European Society of Cardiology (2003 ESH–ESC) guidelines and to compare self-measured blood pressure at home (HBP) with casual-screening blood pressure (CBP) for prediction of first stroke among a general Japanese population.

Methods and results HBP and CBP were measured in 1702 subjects (≥40 years) who had no history of stroke and who were followed for an average of 11 years. The subjects were assigned to one of five groups with differential risk stratification according to the 2003 ESH–ESC criteria: average risk, low added risk, moderate added risk, high added risk, and very high added risk. Even in the low risk group a significantly high risk for stroke was observed, and there was a linear step up of stroke risk based on HBP, as well as on CBP. On the basis of HBP classification, a higher stroke incidence was observed in the high and very high groups compared with CBP classification.

Conclusion The risk stratification system proposed in the 2003 ESH–ESC guidelines is valid for the prediction of stroke in this Japanese study population, and has a stronger predictive power when based on HBP than on CBP. The results indicate the usefulness of HBP for the prediction of stroke risk in individuals.

Introduction

Hypertension is an important risk factor for cardiovascular disease (CVD), which is the second leading cause of death in Japan. Although overall reduction of absolute risk factors for CVD is the goal, blood pressure (BP) management remains a key factor. Thus, accurate diagnosis and treatment of hypertension is necessary for better individual prognosis.

High reproducibility and reliability of self-measurement of BP at home (HBP) have been reported. HBP monitoring is well accepted by patients[1,2] and encourages active participation in the management of personal health conditions. Adjustment of antihypertensive medication based on HBP instead of casual-screening BP (CBP) could lead to lower costs.[3] Moreover, our previous study showed the strong predictive power of HBP measurement for CVD mortality,[4] as HBP avoids observer and regression dilution biases and eliminates the white-coat effect.[2]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[5] emphasized simplified risk stratification. The 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension (2003 ESH–ESC) followed the concepts of the 1999 World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines,[6] stating that comprehensive risk stratification is the essential strategy for the management of hypertension. The

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2003 ESH-ESC guidelines emphasized the importance of individualized medications.

Although the 2003 ESH-ESC guidelines would possibly be applicable even for populations outside Europe,[7] the usefulness of the guidelines in non-European countries has not yet been established. Also, the advantages of HBP measurements when compared with CBP have not been established, especially in terms of predicting first onset of stroke.

One aim of the present study was to examine whether the 2003 ESH-ESC classification was applicable to predict the risk of first stroke incidence, particularly because there is a high incidence of stroke observed among the Japanese.[8] Another aim was to compare the predictive power of HBP and CBP for stroke risk with the stratification system of the 2003 ESH-ESC guidelines. Finally, we compared the prediction of first stroke based on the simplified risk stratification suggested by JNC-7[9] with prediction based on the comprehensive risk stratification from the 2003 ESH-ESC guidelines.

Methods

Study population

The present study was a part of the longitudinal observational study. Subjects have been participating in our HBP measurement project in Ohasama, a rural community in the northern part of Japan, since 1987. The study protocol 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 complies with the Declaration of Helsinki. Informed consent was obtained from each subject.

The socio-economic and demographic characteristics of this region and the details of the selection procedure of study populations have been previously described.[4,10-12] Briefly, HBP measured three times or more and CBP measurements were obtained from 1789 representative individuals of the 1989 eligible individuals aged 40 years or over. As 87 individuals had a previous history of stroke, they were excluded from the present analysis in order to examine the relationship between the first onset of stroke and the risk stratification system of the 2003 ESH-ESC guidelines. Therefore, the study population consisted of 1702 individuals. The mean (SD) age was 60.6 (10.7) years. The ratio of men to women was 39:61, and the reasons for this disproportionate ratio were previously described.[12]

Blood pressure measurements

Physicians and well-trained public health nurses conducted health education classes to inform the subjects on how to measure and record HBP. After their ability to measure HBP was verified, subjects were asked to measure their own HBPs in the sitting position every morning within 1 h after awaking and after ≥2 min of rest and to record the measurements for 4 weeks. All subjects were instructed to position their cuff-covered arms at heart level during HBP measurements. If individuals were taking antihypertensive medications, HBP was measured before taking medications. These procedures were described in detail in our previous report,[10] and were developed according to the guidelines for self-monitoring of HBP.[2] HBP was measured using the HEM 401C (Omron Healthcare Co. Ltd, Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric principle, which generates a digital display of both systolic and diastolic BP.[13]

Annual health check-ups are available to all Japanese citizens aged 40 or over. Subjects are seated at rest for at least 2 min, then CBP is consecutively measured two times by nurses or technicians. A semi-automatic BP measuring device (USM700F; Ueda Electronic Work Co., Ltd, Tokyo, Japan) based on the microphone method was used.

The average arm circumference for subjects was typically <34 cm, so we used a standard arm cuff for both HBP and CBP measurements. The devices for measurement of CBP and HBP were calibrated before the start of the study.[13] All devices met the criteria set by the Association for the Advancement of Medical Instrumentation.[14]

Classification of groups

On the basis of the 2003 ESH-ESC risk stratification system, the subjects were first classified into six BP categories as shown in *Table 1*. HBP-based and CBP-based criteria were defined as follows: optimal (HBP <115/75 mmHg, CBP <120/80 mmHg); normal (HBP 115/75-124/79 mmHg, CBP 120/80-129/84 mmHg); high normal (HBP 125/80-134/84 mmHg, CBP 130/85-139/89 mmHg); Grade 1 (mild hypertension: HBP 135/85-149/94 mmHg, CBP 140/90-159/99 mmHg); Grade 2 (moderate hypertension: HBP 150/95-164/104 mmHg, CBP 160/100-179/109 mmHg); Grade 3 (severe hypertension: HBP ≥165/105, CBP ≥180/110 mmHg). When a systolic or diastolic BP was in a different category, the subject was assigned to the higher category. The CBP classification was equal to the 2003 ESH-ESC criteria. In the present analysis, hypertension was defined as HBP ≥135/85 mmHg, according to the JNC-VI, JNC-7, and 2003 ESH-ESC guidelines; HBP of 135/

Table 1 Stratification of risk to quantify prognosis

Category definition	Optimal	Normal	High normal	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
CBP-based	≤120/80 (n = 370)	120/80-129/84 (n = 387)	130/85-139/89 (n = 396)	140/90-159/99 (n = 375)	160/100-179/109 (n = 136)	≥180/110 (n = 38)
HBP-based	≤115/75 (n = 432)	115/75-124/79 (n = 390)	125/80-134/84 (n = 378)	135/85-149/94 (n = 362)	150/95-164/104 (n = 111)	≥165/105 (n = 29)
No other risk factors	Average	Average	Average	Low	Moderate	High
1-2 risk factors	Average	Low	Low	Moderate	Moderate	Very high
≥3 risk factors or DM	Low	Moderate	High	High	High	Very high
PHCVD	Moderate	High	Very high	Very high	Very high	Very high

DM, diabetes mellitus; PHCVD, past history of cardiovascular disease; Average, average risk; Low, low added risk; Moderate, moderate added risk; High, high added risk; Very high, Very high added risk.

85 mmHg is equivalent to CBP of 140/90 mmHg. To define other BP levels based on HBP, we postulated that 75, 80, 95, and 105 mmHg of diastolic HBP were equivalent to 80, 85, 100, and 110 mmHg of diastolic CBP, respectively. Then systolic BP levels for HBP were introduced from the rate of subjects from each level of CBP classification. In the present analysis, we did not include the concept of pure systolic hypertension.

The individuals were then stratified into four classes based on the extent of cardiovascular risks: Class 1 (no risk factors), Class 2 (one or two risk factors), Class 3 (more than two risk factors or diabetes mellitus), and Class 4 (past history of CVD). Risk factors were defined as follows: age >55 for males, age > 65 for females, body mass index (BMI) >25 kg/m^2, habitual smoking, and hypercholesterolaemia. Finally, study subjects were assigned to one of five groups, according to the 2003 ESH-ESC criteria: average risk, low added risk, moderate added risk, high added risk, and very high added risk (*Table 1*). Subjects with an optimal BP (optimal) who were not described in the risk stratification table of the original ESH-ESC guidelines were assigned to the average, low, or moderate risk group according to their classes. The average risk group was used as the reference group in the analysis. Subjects classified according to CBP and HBP were analysed separately.

In addition to these criteria, we also used the classification system based on the JNC-7 guidelines as previously reported.[9] Briefly, the subjects were classified into four groups based on HBP or CBP according to the JNC-7 criteria:[5] Group 1 (normotension: HBP <115/75 mmHg, CBP <120/80 mmHg); Group 2 (prehypertension: HBP 115/75–134/84 mmHg, CBP 120/80–139/89 mmHg); Group 3 (Stage 1 hypertension: HBP 135/85–149/94 mmHg, CBP 140/90–159/99 mmHg); Group 4 (Stage 2 hypertension: HBP ≥150/95 mmHg, CBP ≥160/100 mmHg). After classification of BP values, Groups 2–4 were divided into two subgroups—'a' and 'b'—indicating those without and those with CVD risks (diabetes, hypercholesterolaemia, habitual smoking, or history of CVD), respectively. All subjects were assigned to one of seven categories (Groups 1, 2a, 3a .. 4b) based on the JNC-7 classification.

Follow-up and risk ascertainment

We accumulated follow-up data until 31 December 2001. The subjects' residence status in Ohasama was confirmed by registration cards. These cards are accurate and reliable because they are used for pensions and social security benefits in Japan. Twenty-seven subjects (1.8%) had moved away and were eliminated from follow-up, and 209 deaths (14.0%) were identified from the residents' registration cards.

The incidence and past history of stroke were investigated through the Stroke Registration System of Iwate Prefecture, death certificates, receipt of National Health Insurance, and questionnaires sent to each household at the time of HBP measurement. The information was then confirmed by checking the medical records of Ohasama hospital where >90% of the subjects nad their regular check-ups. We used computed tomography (CT) scans and magnetic resonance imaging (MRI) reports to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. The analysis included only the first event in those who had multiple non-fatal events. The diagnostic criteria of stroke and their subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.[15]

Other information for individuals such as height, weight, habitual smoking, use of antihypertensive medication at baseline, history of heart disease, hypercholesterolaemia, or diabetes mellitus was obtained from questionnaires sent to each household at the time of HBP measurements, from records of annual health check-ups, and from medical records at Ohasama Hospital. Subjects using lipid-lowering drugs or those with serum cholesterol levels of ≥5.68 mmol/L (220 mg/dL) were considered to have hypercholesterolaemia. Subjects with a fasting glucose level of ≥7.77 mmol/L (140 mg/dL) or non-fasting glucose level of ≥11.11 mmol/L (200 mg/dL), or those using insulin or oral antihyperglycaemic drugs were defined as having diabetes mellitus. A past history of CVD included a history of myocardial infarction, angina pectoris, atrial fibrillation, or cardiac failure.

Data analysis

The HBP values were the average of all home measurements per subject. CBP of each subject was the average of two consecutive CBP readings taken at the beginning of the study.

The risk of the first stroke was examined using the Cox proportional hazards model. The dependent variable was the number of days from the initial HBP measurement to the date of stroke or censoring. Stroke-free survivors as of December 31, 2001 were censored. The independent variables were the groups of the risk stratification system using the 2003 ESH-ESC guidelines in which factors of age and sex were included. In further analysis, the risk in relation to the JNC-7 guideline-based classification was examined by the Cox model adjusted for age and sex. When we analysed the incidence of stroke, we censored cases of death from causes other than fatal stroke events.

The estimated relative hazard (RH) and the 95% confidence interval (95% CI) of variables were derived from the coefficient and standard error determined by the Cox proportional hazards model. The RH is expressed relative to Group 1 (average risk; RH = 1). Separate models were used for HBP classification and CBP classification after verification of the assumption of proportionality for the Cox proportional hazards models.[16] The predictive values of HBP classification and CBP classification were evaluated using the comparison of corresponding regression coefficients and log likelihoods in the Cox model. We also assessed the interaction between antihypertensive medication and the five risk groups using the Cox model with stroke as the endpoint. All data are shown as mean (SD) unless otherwise stated. A P-value <0.05 (two-sided test) was accepted as indicative of statistical significance. The SAS system (Version 8.2, SAS Institute Inc., Cary, NC, USA) was used for all statistical calculations.

Results

The subjects were followed up for a median of 10.9 (interquartile 8.9–13.9) years, to a maximum of 13.9 years. We obtained 149 incident cases of first stroke among the 1702 individuals: 106 (69%) cerebral infarction, 28 (18%) intracerebral haemorrhage, 12 (8%) subarachnoid haemorrhage, and 3 (2%) unknown causes. In addition to 149 stroke cases, four incidences of transient ischaemic attack were observed, and excluded from the analysis. There was no interaction between the use of antihypertensive medication and the five risk groups (HBP, $P = 0.7$; CBP, $P = 0.4$).

The characteristics of the subjects are shown in *Table 2*. Of the 1702 study subjects, 370 (22%) were classified as current or ex-smokers; 507 (30%) were treated with antihypertensive medication at baseline; 16 (1%) had a history of heart disease; 218 (13%) had diabetes mellitus, and 207 (12%) had hypercholesterolaemia. The mean number of HBP measurements from each individual was 23.0 (7.1). The mean systolic and diastolic HBP of all subjects were 125.2 (15.0) and 74.9 (10.1) mmHg, respectively.

The risk of first stroke of the five groups in HBP classification and CBP classification is shown in *Figure 1A and B*. Stroke risk was increased linearly, with the increase in the grade of stratified risk based on HBP, as well as on CBP. Even in the low risk group, the risk for stroke was

Table 2 Clinical characteristics among groups

Variables	Average	Low	Moderate	High	Very high
Home blood pressure based groups					
Number of subjects	584	543	377	160	38
Age (years)	54.9 ± 9.1	61.5 ± 9.8	65.5 ± 10.6	64.5 ± 9.1	68.2 ± 11.0
Male (%)	23.8	42.2	52.5	50.0	63.2
BMI (kg/m^2)	22.4 ± 2.4	23.7 ± 3.1	23.6 ± 3.2	25.0 ± 3.3	24.1 ± 4.7
PH CVD (%)	0	0	0	3.8	26.3
Diabetes (%)	0	8.3	11.9	75.6	18.4
Smoking (%)	8.9	27.8	26.8	33.1	34.2
Hypercholesterolaemia (%)	3.1	12.7	11.9	43.1	15.8
Use of antihypertensive medication (%)	11.8	26.2	46.9	60.0	60.5
Home SBP (mmHg)	112.6 ± 8.8	123.5 ± 8.2	138.8 ± 11.5	137.2 ± 10.1	157.1 ± 16.8
Home DBP (mmHg)	68.0 ± 7.2	74.1 ± 6.9	82.0 ± 9.1	81.9 ± 9.1	92.3 ± 13.6
Casual SBP (mmHg)	124.3 ± 16.2	132.4 ± 17.1	142.2 ± 18.2	140.9 ± 18.5	151.1 ± 23.8
Casual DBP (mmHg)	72.0 ± 10.5	74.9 ± 10.8	80.0 ± 11.9	79.8 ± 12.7	83.4 ± 13.3
Casual blood pressure based groups					
Number of subjects	529	564	408	158	43
Age (years)	55.1 ± 8.5	61.3 ± 10.7	64.9 ± 10.7	63.6 ± 9.3	65.2 ± 12.3
Male (%)	24.0	45.2	46.1	51.3	44.2
BMI (kg/m^2)	22.3 ± 2.2	23.5 ± 3.1	24.0 ± 3.4	24.8 ± 3.5	24.0 ± 3.1
PH CVD (%)	0	0	1.0	1.3	23.3
Diabetes (%)	0	5.9	11.8	82.3	16.3
Smoking (%)	11.3	27.3	24.5	29.7	20.9
Hypercholesterolaemia (%)	2.6	11.2	15.4	36.1	23.3
Use of antihypertensive medication (%)	14.2	26.1	45.8	47.5	53.5
Home SBP (mmHg)	115.5 ± 11.2	124.8 ± 13.0	133.9 ± 14.3	132.3 ± 14.5	140.6 ± 15.1
Home DBP (mmHg)	70.1 ± 8.6	75.0 ± 8.9	78.9 ± 10.4	78.6 ± 10.2	82.0 ± 11.7
Casual SBP (mmHg)	117.0 ± 11.2	130.2 ± 10.0	148.0 ± 14.9	146.1 ± 15.1	176.9 ± 22.1
Casual DBP (mmHg)	68.5 ± 8.4	74.4 ± 9.4	82.5 ± 11.6	81.3 ± 10.2	94.3 ± 14.5

See *Table 1* for definitions of groups. Values are expressed as mean ± SD. CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure.

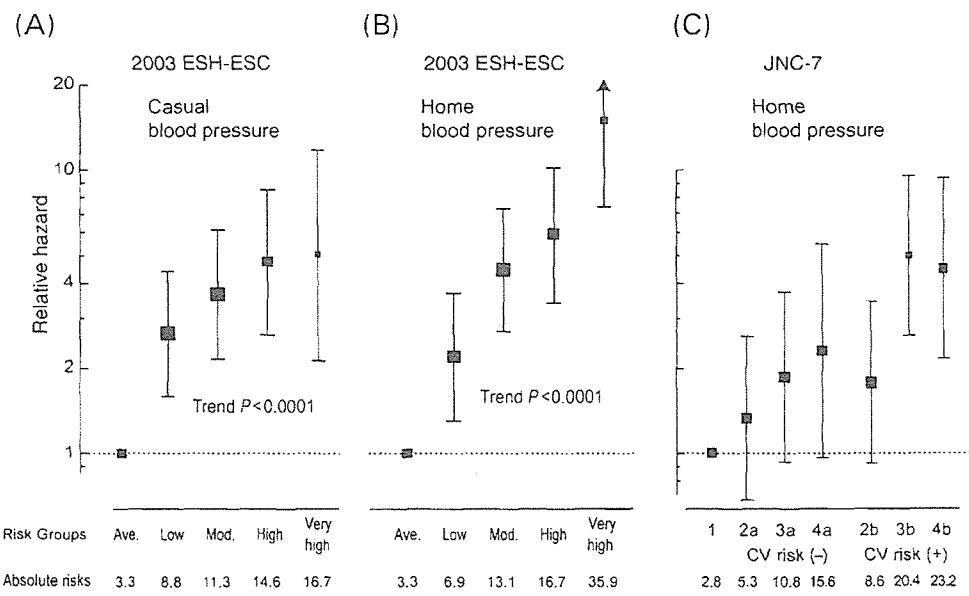

Figure 1 Risk of first stroke based on HBP or CBP values and cardiovascular risks. (*A*) and (*B*) demonstrate RH and 95% CI for first stroke plotted on a log scale among all groups classified by CBP (*A*) and HBP (*B*) values. Ave.: average risk group, Low: low added risk group, Mod.: moderate added risk group, High: high added risk group, Very High: very high added risk group. (C) demonstrates RH and 95% CI for first stroke according to JNC-7 classification based on HBP values. Absolute risks display incidence per 1000 person-years. Group definitions are shown in *Table 1* and in the Methods section. The average group (2003 ESH–ESC) or Group 1 (JNC-7) is treated as the reference category. Solid squares indicate the RH point and are sized in proportion to the number of events observed. Vertical lines extending from squares represent 95% CI. Trend *P*-values express the linearity among groups.

significantly higher than in the average risk group. In the low risk group, there was no difference in the stroke risk between HBP classification and CBP classification (HBP: RH = 2.24, 95% CI 1.32-3.80, $P = 0.003$; CBP: RH = 2.76, 95% CI 1.63-4.66, $P = 0.0001$). The stroke risk in the very high risk group was extremely high when subjects were classified by HBP (RH = 14.4, 95% CI 6.92-29.8, $P < 0.0001$). The predictive power decreased when subjects were classified by CBP (RH = 5.30, 95% CI 2.23-12.6, $P = 0.0002$). The statistically significant linearity among the groups was observed for both HBP and CBP classifications (trend $P < 0.0001$). When we designated the low risk group as a reference category in the Cox model, the stroke risk in the moderate risk group was significantly high for HBP (RH = 2.04, 95% CI 1.34-3.09, $P = 0.0009$), whereas the moderate risk group was not significantly different from the low risk group using the CBP classification (RH = 1.33, 95% CI 0.90-1.97, $P = 0.2$). When both classifications were treated as continuous variables and were simultaneously included in the model, only HBP classification was significantly related with stroke risk (HBP classification: RH = 1.88, 95% CI 1.55-2.28, $P < 0.0001$; CBP classification: RH = 0.98, 95% CI 0.81-1.20, $P = 0.9$). The model, including both HBP and CBP classifications, lost 'goodness of fit' when HBP was removed (likelihood ratio 40.2, $P < 0.001$), whereas no significant changes occurred when CBP was removed (likelihood ratio 0.028, $P = 0.9$). The same results were observed when transient ischaemic attack was included in the stroke incidence (data not shown).

We conducted further analysis by comparing the JNC-7 guideline-based classification (including subarachnoid haemorrhage and excluding transient ischaemic attack which was a modified analysis from our previous study[9]) and the 2003 ESH-ESC guideline-based classification (*Figure 1B and C* based on HBP). The stroke risk in Group 4b (highest) was significantly elevated for HBP classification (RH = 4.54, 95% CI 2.16-9.54, $P < 0.0001$) as well as for CBP (RH = 2.81, 95% CI 1.31-6.04, $P = 0.008$). However, for the magnitude of RH, the stroke risk based on the 2003 ESH-ESC classification was clearly more dramatic than that based on the JNC-7 classification.

Discussion

The 2003 ESH-ESC guidelines for treating hypertension emphasize a composite risk stratification system based on CBP categories and other risk factors. In this prospective cohort study, we found that the 2003 ESH-ESC classification was useful and applicable for a general Japanese population in predicting future stroke incidence. Furthermore, the risk stratification system became extremely powerful for the prediction of stroke incidence when HBP was used instead of CBP. These results were based on a comprehensive follow-up system in the Ohasama cohort as described previously and the high reliability of diagnoses of stroke and subtypes according to CT/MRI. Although some of the stroke cases were determined by death certificates only, these were limited to 3% of the total cases. Although some of the risk parameters from the 2003 ESH-ESC guidelines were not evaluated, it is a reasonable assumption that the predictive power of HBP as well as CBP would be emphasized if those unmeasured parameters were included in our analysis. Thus, the results support the usefulness of the 2003 ESH-ESC guidelines for the general Japanese population, especially when information on BP is based on HBP.

In comparison with the 2003 ESH-ESC guidelines, the JNC-7 classification adopts a simplified risk stratification that consists of four grades based on CBP.[5] Individuals who have hypertension and at least one risk factor are considered to be candidates for antihypertensive drugs and intensive treatment. Thus their cardiovascular risks are not thoroughly considered in JNC-7. We reported in the previous study that the JNC-7 classification is applicable for the general Japanese population.[9] However, when based on the risk stratification system proposed in the 2003 ESH-ESC guidelines, the measurements of HBP as well as CBP would predict the first stroke incidence more accurately than those based on the simplified risk stratification in JNC-7 as shown in the current study (refer to Asayama *et al.*[9]). It is a reasonable assumption that a comprehensive risk stratification system could be used for individualized BP management. Furthermore, we would like to emphasize that in this study, the stroke risk in the moderate risk group was significantly higher than that in the low risk group when based on HBP, whereas no significant differences were observed between two risk groups when based on CBP; these findings support the assertion that BP management should be based on HBP information.

The 2003 ESH-ESC guidelines set the reference value of hypertension using HBP at 135/85 mmHg. In the present study, hypertension was also defined as HBP at 135/85 mmHg, then HBP was classified by the percentage distribution of subjects according to the corresponding ratio of CBP. A stepwise increase of stroke risk in the stratification system was observed when based on HBP as well as CBP in the current study. It should be noted that high-normal individuals and prehypertension have relatively high CVD risk when compared with individuals with optimal[17] or normal BP.[18] Hypothetically speaking, the lower the BP, the better the stroke prevention.[19]

Approximately one-quarter of our subjects with high-normal BP (23.5% based on HBP and 22.5% based on CBP) were classified as average risk according to the 2003 ESH-ESC guidelines. There were 89 high-normal BP subjects among 584 (HBP-based) and 89 high-normal subjects among the 529 (CBP-based) average risk subjects. A major difference between the 2003 ESH-ESC and JNC-7 guidelines is that the latter advises pharmacological or non-pharmacological intervention in all prehypertensives (high-normal or normal BP), whereas the former suggests intervention only for those who are in the low added risk but not in the average risk' category.[20] According to our results, it was obvious that individuals in the low risk group needed treatment even though their BP was within normal limits, whereas treatment for the average risk individuals remains a matter for debate.

Although HBP measurement is now acknowledged worldwide in the major guidelines as a useful tool for clinical practice, lack of information on the prognostic significance has limited its use in clinical decision-making.[5,6,21-23] In the present study, we demonstrated that HBP measurements provide more useful prognostic information on cerebrovascular disease than CBP measurements. Information on BP in relation to the time of day, as well as an increased number of measurements, improves the quality of data. Furthermore, HBP is usually measured under more

controlled conditions than CBP. The average of multiple values of HBP obtained under controlled conditions provides individual BP information without biases such as white-coat effect, regression dilution biases, and time effect.[2]

In conclusion, the risk stratification system proposed in the 2003 ESH-ESC guidelines was valid for the prediction of stroke incidence in populations outside Europe, and we found that the stratification based on HBP measurements is a valuable tool for predicting the incidence of stroke. Guidelines based on individualized medications, such as the 2003 ESH-ESC guidelines, are more useful and applicable than those based on simple BP-oriented medications, such as the JNC-7. HBP measurement is a useful tool to improve awareness of hypertension and to predict future incidence of cerebrovascular disease.

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2. 白衣高血圧と将来の家庭高血圧発症との関連

別添論文

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要約

随時血圧と家庭血圧の双方が高血圧を示す持続性高血圧とは対照的に、随時血圧において高血圧を示すが、家庭血圧は正常域にあるような状態を‘白衣高血圧’という。しかしながら、家庭血圧正常者において白衣高血圧と将来の家庭高血圧発症との関連を検討したものはなかった。

岩手県大迫町の 40 歳以上の一般住民のうち、ベースライン調査時（1988-1993）に家庭血圧を 3 回以上測定し、かつ随時血圧を測定した家庭正常血圧者（降圧薬非服用かつ HBP＜135/85mmHg） 912 名を対象とした。本検討では、家庭正常血圧者のうち、随時血圧＜140/90mmHg かつ家庭血圧＜135/85mmHg の者を真性正常血圧、それ以外を白衣高血圧とした。持続性高血圧発症の定義は、家庭血圧で収縮期 135mmHg 以上または拡張期 85mmHg 以上への進展、もしくは降圧薬の服用開始とした。

ベースライン調査時に家庭血圧正常者であった 912 名中、777 名（平均 56 歳、男性 34%）が平均 8 年後に家庭血圧再測定を行った（追跡率 85%）。 真性正常血圧群 649 名中 144 名（22%）、白衣高血圧群 128 名中 60 名（47%）が、それぞれこの間に持続性高血圧に移行した。 真性正常血圧群に対する、白衣高血圧群の持続性高血圧移行オッズ比は、 2.86 （95%信頼区間: 1.90－4.31）と有意に高値であり、白衣高血圧の存在は、性・年齢・body mass index とともに、独立した持続性高血圧発症のリスク因子であった。

本研究から、白衣高血圧が全く無害ではなく、将来の高血圧発症の予測因子であることが明らかとなった。これは、将来の高血圧の発症、及び高血圧合併症の発生を予防するために、白衣高血圧者について定期的な経過観察を行うことの必要性を示唆するものである。