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Relation of Blood Pressure and All-Cause Mortality in 180 000 Japanese Participants

Pooled Analysis of 13 Cohort Studies

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Abstract—Hypertension is a leading cause of death because of cardiovascular disease and predominantly affects total mortality. To reduce avoidable deaths from hypertension, we need to collect blood pressure data and assess their impact on total mortality. To examine this issue, a meta-analysis of 13 cohort studies was conducted in Japan. Poisson regression was used for estimating all-cause mortality rates and ratios. In the model, blood pressure data were treated as continuous (10-mm Hg increase) and categorical (every 10 mm Hg) according to recommendations of the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension. Potential confounders included body mass index, smoking, drinking, and cohort. The impact of hypertension was measured by the population-attributable fraction. After excluding participants with cardiovascular disease history, 176 389 participants were examined in the analysis. Adjusted mortality rates became larger as the blood pressure increased, and these were more distinct in younger men and women. Hazard ratios also showed the same trends, and these trends were more apparent in younger men (hazard ratio [unit: 10-mm Hg increase] aged 40 to 49 years: systolic blood pressure 1.37 (range: 1.15 to 1.62); diastolic blood pressure 1.46 [range: 1.05 to 2.03]) than older ones (hazard ratio: aged 80 to 89 years: systolic blood pressure 1.09 [range: 1.05 to 1.13]and diastolic blood pressure 1.12 [range: 1.03 to 1.22]). Population-attributable fraction of hypertension was ≈20% when the normal category was used as a reference level and was 10% when we included the prehypertension group in the reference level. In conclusion, high blood pressure raised the risk of total mortality, and this trend was higher in the younger Japanese population. (***Hypertension.*** **2008;51:1483-1491.)**

Key Words: pooled analysis ■ total mortality ■ cohort study ■ blood pressure ■ population attributable fraction

High blood pressure is a well-established leading cause of cardiovascular disease mortality. The contribution of hypertension to total mortality is also large,[1] and the importance of management of hypertension is widely accepted not only in clinical practice but also in public health practice. Before measures for reducing hypertension are implemented, more information about the relationship between hypertension and total mortality is needed. For example, one study found that the hazard ratio of cardiovascular disease in those with high blood pressure was larger in younger than in older participants,[2] suggesting that the contribution of high blood pressure to mortality differed at different ages. The examination of this important issue requires a large number of participants, and a single cohort study estimating this contribution is limited by small sample size. The Joint National Committee of Hypertension 7 (JNC-7) also mentioned the importance of the risk of mortality and the contribution of prehypertension to total mortality.[3] The relation between blood pressure and total mortality is, therefore, of great interest. It is difficult to address this issue in a single cohort study, because few events can be observed in cohorts subgrouped, eg, by age or prehypertension status. A large-scale cohort study could answer these questions, but the huge amount of cost and effort involved represent serious obstacles. Meta-analysis using data on individual participants[4] is an efficient way to deal with this issue, and the approach has been used in studies of cardiovascular disease epidemiology.[2,5,6]

In Japan, meta-analysis of individual participants' data for cardiovascular disease was conducted in the Japanese population. The study, called Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN), included 13 cohort studies of existing Japanese cohorts. The total number of EPOCH-JAPAN participants was 188 321, with ≈10 years of follow-up. The purpose of this study was to examine sex- and age-specific hazard ratios and the effect of blood pressure on total mortality and to estimate the contribution of high blood pressure to all-cause death by

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Table 1. Baseline Characteristics of Study Participants in Each Cohort: EPOCH-JAPAN

Cohort Name	Geographic Location (Prefecture)	Source of Baseline Survey, Year, Reference(s)	Follow-Up Periods		No. of Participants	Age at Study Entry		Blood Pressure			
								Systolic		Diastolic	
			Average	SD		Average	SD	Average	SD	Average	SD
Men											
Tanno-Sobetsu	Hokkaido	1977[7,8]	18	5	840	51	7	132	20	82	10
Osaki	Miyagi	1994[9]	6	1	6918	63	10	133	17	80	11
Ohasama	Iwate	1987[10]	10	3	1122	61	11	135	17	76	11
Oyabe	Ishikawa	1988[11]	10	2	1509	61	10	131	20	79	11
YKK workers	Toyama	1990[12]	11	2	3177	51	6	121	15	74	12
SPMI cohort	Shiga	1989–1991[13]	9	3	1939	54	8	133	18	81	11
Suita	Osaka	1989[14,15]	6	2	2339	60	11	131	21	80	12
RERF cohort	Hiroshima	1986[16]	14	5	1506	60	13	135	22	85	12
Hisayama	Fukuoka	1988[17]	10	3	1113	58	12	135	20	81	11
JACC study	Nationwide‡	1988–1990[18]	9	2	11 041	58	10	135	19	81	11
NIPPON DATA80	Nationwide‡	1980[19]	16	5	3161	56	11	142	22	85	12
NIPPON DATA90	Nationwide‡	1990[20]	9	2	2759	57	11	140	20	85	12
Ibaraki	Ibaraki	1993[21,22]	10	2	33 134	61	10	137	17	81	11
Total			10	3	70 558	60	10	135	19	81	11
Women											
Tanno-Sobetsu	Hokkaido	1977[7,8]	18	4	971	51	7	134	20	82	10
Osaki	Miyagi	1994[9]	6	1	9312	62	9	130	18	78	11
Ohasama	Iwate	1987[10]	10	2	1678	60	10	130	17	73	11
Oyabe	Ishikawa	1988[11]	10	1	3208	58	10	126	20	75	11
YKK workers	Toyama	1990[12]	11	2	1724	50	6	115	15	70	11
SPMI cohort	Shiga	1989–1991[13]	9	3	2596	55	8	132	17	79	10
Suita	Osaka	1989[14,15]	6	2	2619	58	11	129	22	77	12
RERF cohort	Hiroshima	1986[16]	15	5	3121	63	12	135	23	81	12
Hisayama	Fukuoka	1988[17]	11	3	1518	59	12	133	22	76	11
JACC study	Nationwide‡	1988–1990[18]	10	2	19 210	57	9	132	19	78	11
NIPPON DATA80	Nationwide‡	1980[19]	17	4	4020	56	11	139	22	81	12
NIPPON DATA90	Nationwide‡	1990[20]	10	2	3697	58	12	138	20	81	12
Ibaraki	Ibaraki	1993[21,22]	10	2	63 909	59	10	132	18	78	11
Total			10	3	117 583	58	10	132	19	78	11

(*Continued*)

*In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-smokers were classified as never-smokers.
†In the studies of Tanno-Sobetsu, Ohasama, and Oyabe, ex-drinkers were classified as never-drinkers.
‡In this nationwide cohort study, study participants were from all areas of Japan.

performing a meta-analysis of the data from 13 population-based cohort studies conducted in Japan.

Study Participants and Methods

Study Cohorts

The EPOCH-JAPAN Study is the pooled analysis of 13 cohort studies examining the relation between health measures (laboratory measures and lifestyle and behavioral factors) and disease (mortality and incidence) in the Japanese population. The criteria for inclusion of meta-analysis were as follows: collection of health examination measures, follow-up of ≈10 years, and a number of participants >1000 persons. Both nationwide and single-site cohort studies were included. The name of each cohort study[7–22] is listed in Table 1. Inclusion criteria for participants were age at entry (40 to 90 years old) and availability of information about sex, age at entry, systolic blood pressure, and diastolic blood pressure. Since the end of follow-up varied between cohorts, we limited age ranges of follow-up from 40 to 90 years, and the end of the observation period was set at age 90 years.

Statistical Methods

Hazard ratios for total mortality were estimated in men and women separately. Participants were stratified into 10-year age groups from 40 to 80 years, and a statistical model was made to analyze the data of each age group separately. They were also divided on the basis of systolic blood pressure (SBP) into 10-mm Hg groups from <120 mm Hg to ≥160 mm Hg and on the basis of diastolic blood pressure (DBP) into 10-mm Hg groups from <70 mm Hg to ≥100 mm Hg. The lowest blood pressure group (<120 mm Hg for SBP and <70 mm Hg for DBP) served as the reference group.

A Poisson regression model was constructed for each sex and age group. When we analyzed the sex-combined results, we included sex in the model. In the model, we analyzed continuous and categorical

Table 1. Continued

Smoking Status*				Drinking Status†				Body Mass Index		No. of All-Cause Mortality
Never	Past	Current	Missing	Never	Past	Current	Missing	Average	SD	
228	0	522	90	214	0	533	93	23	3	130
1413	1996	3188	321	1048	556	5114	200	24	3	548
585	0	537	0	459	0	663	0	23	3	250
689	0	820	0	392	416	701	0	23	3	270
809	494	1874	0	562	38	2577	0	23	3	73
544	229	1164	2	398	0	1529	12	23	3	150
423	772	1105	39	504	99	1699	37	23	3	169
191	417	721	177	203	86	963	254	22	3	614
228	329	556	0	369	70	673	1	23	3	180
2392	2639	5590	420	2074	572	8069	326	23	3	1402
578	655	1922	6	657	219	2279	6	22	3	994
605	708	1446	0	962	206	1591	0	23	3	412
7376	9190	16 567	1	9629	2039	21 465	1	23	3	4688
16 061	17 429	36 012	1056	17 471	4301	47 856	930	23	3	9880
804	0	65	102	792	0	76	103	24	3	85
6706	120	355	2131	5617	225	1646	1824	24	3	302
1639	0	39	0	1584	0	94	0	24	3	194
3126	0	82	0	2770	399	39	0	23	3	255
1693	9	22	0	1320	7	397	0	22	3	18
2467	14	87	28	2049	0	520	27	23	3	65
2173	87	279	80	1727	39	783	70	23	3	85
2602	96	296	127	1605	47	951	518	23	4	889
1382	31	105	0	1366	17	133	2	23	3	123
16 989	208	656	1357	14 559	223	3535	893	23	3	997
3573	91	352	4	3236	59	717	8	23	3	790
3284	87	326	0	3443	35	219	0	23	3	312
60 357	462	3088	2	57 783	125	5999	2	24	3	3762
106 795	1205	5752	3831	97 851	1176	15 109	3447	24	3	7877

blood pressure data to estimate the hazard ratio. Body mass index, smoking status (smokers, ex-smokers, or never-smokers), drinking status (drinkers, ex-drinkers or never-drinkers), and cohort were included in the model as confounders. Person-years of observation was separated into 5 categories (1 for every 10 years from age 40 to age 80 years) and used as an offset variable in Poisson regression. Multivariate adjusted mortality rates were estimated from the Poisson regression. Mortality rates among groups were calculated after adjusting for the population-averaged effects of confounders (eg, smoking, drinking, and mean body mass index).

The MacMahon and Peto method was used to correct for regression dilution bias of blood pressure.[4,23] The dilution factors of blood pressure were derived from longitudinal blood pressure measurements made by the Ohasama Study that followed 1900 participants from 1999 to 2002. From the data, the calculated regression dilution ratio was 0.59 for SBP and 0.48 for DBP. Hazard ratio for total mortality according to the JNC-7 definition was also estimated in the analysis. The prehypertension (120≤SBP<140 mm Hg or 80≤DBP<90 mm Hg), hypertension stage 1 (140≤SBP<160 mm Hg or 90≤DBP<100 mm Hg), and hypertension stage 2 (160 mm Hg≤SBP or 100 mm Hg≤DBP) groups were compared with the normal reference groups (<120 mm Hg for SBP and <80 mm Hg for DBP).

The population-attributable fraction of high blood pressure according to the JNC 7 classification was calculated from the hazard ratio. Two reference levels (the normal and below prehypertension [normal plus prehypertension]) and the excess hazard ratio were used to calculate the population-attributable fraction. The prevalence of hypertension was set as the total number of participants in this study.[24] All of the statistical analysis was performed using SAS release 9.13 (SAS Institute Inc).

Results

Table 1 shows baseline characteristics of participants in each cohort. There were 188 141 participants (men: 70 558; women: 117 583). Average age at study entry was 59.6 years in men and 58.4 years in women, and the average follow-up

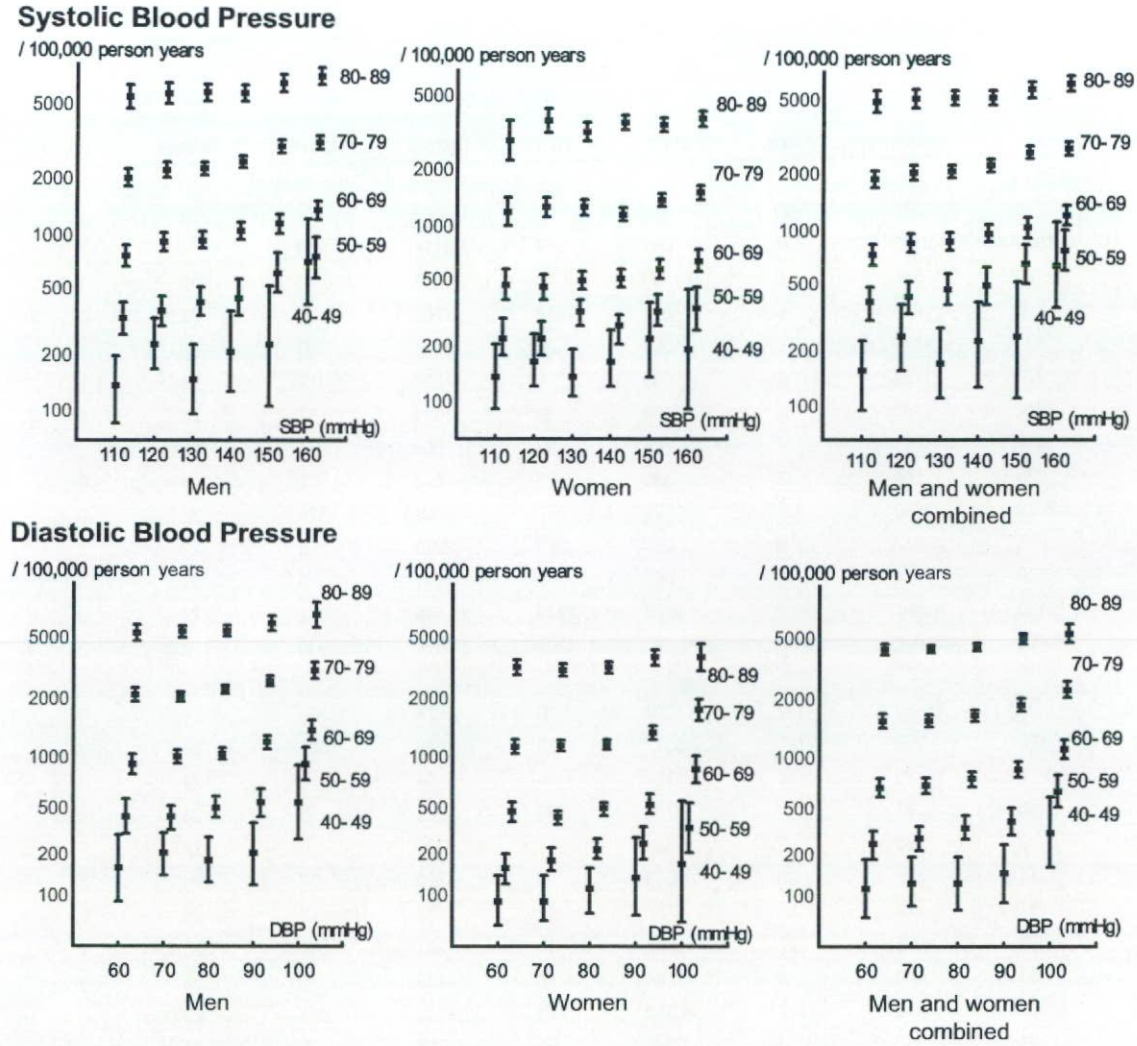

Figure. Relation between blood pressure and multivariate-adjusted mortality rate by age range. Each dot represents a multivariate estimate of mortality rate after adjusting for smoking, drinking, and body mass index, and each line shows the 95% CI. The number of events in each age category are as follows: men aged 40 to 49 years: 137; age 50 to 59 years: 566; age 60 to 69 years: 1900; age 70 to 79 years: 3782; age 80 to 89 years: 2183; women aged 40 to 49 years: 128; age 50 to 59 years: 518; age 60 to 69 years: 1392; age 70 to 79 years: 2708; age 80 to 89 years: 2258.

period was 9.6 years in men and 9.9 years in women. The total number of deaths (all-cause) was 17 757 (men: 9880; women: 7877). The characteristics of the cohorts were similar, and no apparent differences in hazard ratio were found at each blood pressure level. In our study, we analyzed participants without cardiovascular disease history. Because there was no information of cardiovascular disease history in the Tanno-Sobetsu cohort, we excluded these participants, and, therefore, 176 389 (male: 65 463; female: 110 926) participants were investigated in our study.

The Figure shows the relation between blood pressure and multivariate-adjusted hazard rate for total mortality. In almost every age group, mortality rate was higher at a higher SBP level and higher DBP levels. The difference in absolute mortality rate between the highest and lowest blood pressure groups was larger in older than in younger participants. The results did not change even when we excluded the participants who did not take antihypertensive medication.

Table 2 shows the multivariate-adjusted mortality ratio for all-cause mortality for each 10-mm Hg blood pressure increase. In all of the age groups and categories, the hazard ratios were statistically significant. The hazard ratio was larger in the younger group than in the older group. The effect of modifying age was apparent when we included the interaction terms of age and blood pressure into the model (men: $P<0.01$ in both SBP and DBP; women: $P=0.02$ in SBP and $P=0.05$ in DBP). Although we excluded body mass index or alcohol drinking from confounding factors, our result did not changed largely.

Table 3 shows the multivariate-adjusted hazard ratio for all-cause mortality according to JNC-7 criteria. Although they fluctuated in some categories to some extent, hazard ratio gradually increased in all of the sex and age categories. With some exceptions, the hazard ratio in groups with hypertension was consistently higher for almost every age range in both men and women.

Table 2. Multivariate-Adjusted Hazard Ratio of All-Cause Mortality According to Age and 10-mm Hg Blood Pressure Increase During an Average 9.8 Years of Follow-Up

Sex	Age Category, y	No. of Deaths	SBP Hazard Ratio (95% CI)	DBP Hazard Ratio (95% CI)
Men	40 to 49	137	1.37 (1.15 to 1.62)	1.46 (1.05 to 2.03)
	50 to 59	566	1.23 (1.14 to 1.33)	1.42 (1.21 to 1.65)
	60 to 69	1900	1.16 (1.11 to 1.21)	1.28 (1.17 to 1.40)
	70 to 79	3782	1.14 (1.11 to 1.17)	1.21 (1.13 to 1.29)
	80 to 89	2183	1.09 (1.05 to 1.13)	1.12 (1.03 to 1.22)
Women	40 to 49	128	1.19 (1.00 to 1.41)	1.40 (1.00 to 1.95)
	50 to 59	518	1.16 (1.07 to 1.26)	1.38 (1.17 to 1.64)
	60 to 69	1392	1.21 (1.15 to 1.27)	1.29 (1.16 to 1.44)
	70 to 79	2708	1.12 (1.08 to 1.16)	1.25 (1.15 to 1.35)
	80 to 89	2258	1.07 (1.03 to 1.11)	1.12 (1.03 to 1.22)
Men and women combined	40 to 49	265	1.27 (1.13 to 1.44)	1.42 (1.12 to 1.80)
	50 to 59	1084	1.20 (1.14 to 1.27)	1.40 (1.25 to 1.58)
	60 to 69	3292	1.18 (1.15 to 1.22)	1.29 (1.20 to 1.38)
	70 to 79	6490	1.13 (1.11 to 1.16)	1.22 (1.16 to 1.29)
	80 to 89	4441	1.08 (1.05 to 1.11)	1.12 (1.05 to 1.19)

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking and body mass index. To correct regression dilution bias, parameter estimates were multiplied by regression dilution factors (SBP: 0.59; DBP: 0.48). Unadjusted hazard ratios of SBP were as follows: men aged 40 to 49: 1.21 (1.09 to 1.34), 50 to 59: 1.14 (1.08 to 1.19), 60 to 69: 1.09 (1.07 to 1.12), 70 to 79: 1.08 (1.06 to 1.10), 80 to 89: 1.05 (1.03 to 1.08); women aged 40 to 49: 1.11 (1.00 to 1.23), 50 to 59: 1.10 (1.04 to 1.15), 60 to 69: 1.12 (1.09 to 1.15), 70 to 79: 1.07 (1.05 to 1.09), 80 to 89: 1.04 (1.02 to 1.07); men and women combined aged 40 to 49: 1.16 (1.08 to 1.25), 50 to 59: 1.12 (1.08 to 1.16), 60 to 69: 1.11 (1.09 to 1.13), 70 to 79: 1.08 (1.06 to 1.09), 80 to 89: 1.05 (1.03 to 1.06). Unadjusted hazard ratios of DBP were as follows: men aged 40 to 49: 1.20 (1.02 to 1.40), 50 to 59: 1.18 (1.10 to 1.27), 60 to 69: 1.13 (1.08 to 1.18), 70 to 79: 1.09 (1.06 to 1.13), 80 to 89: 1.06 (1.01 to 1.10); women aged 40 to 49: 1.17 (1.00 to 1.38), 50 to 59: 1.17 (1.08 to 1.27), 60 to 69: 1.13 (1.07 to 1.19), 70 to 79: 1.11 (1.07 to 1.15), 80 to 89: 1.06 (1.01 to 1.10); men and women combined aged 40 to 49: 1.18 (1.06 to 1.33), 50 to 59: 1.18 (1.11 to 1.24), 60 to 69: 1.13 (1.09 to 1.17), 70 to 79: 1.10 (1.08 to 1.13), 80 to 89: 1.06 (1.03 to 1.09).

The population-attributable fraction for each age range was similar in men and women. In men, except for age 80 to 89 years, 10.5%, the population-attributable fraction was ≈20% to 30%. Except for the lowest population-attributable fraction in women aged 40 to 49 and aged 80 to 89 years, the population-attributable fraction was ≈10% to 20%. For the overall population, the population-attributable fraction of nonnormal blood pressure was 22.7% in men and 17.9% in women. The population-attributable fraction became smaller when the reference was the combination of normal and prehypertension groups as compared with the normal group alone.

Discussion

On the basis of a meta-analysis of individual data from 176 389 Japanese participants, we confirmed that high blood pressure affects total mortality in all age categories. We found that there was an apparent effect modification by age and blood pressure and that hazard ratio was higher in younger than in older groups. We also examined the impact of primary prevention of high blood pressure on total mortality by calculating the population-attributable fraction and found that it was considerable in both men and women.

Blood pressure values are known to be relatively higher in Japan than other developed countries. This situation still exists although values have dropped dramatically.[25] One third of Japanese men and women died from cardiovascular diseases,[26] and Japan has one of the highest stroke mortalities among developed countries.[27] Thus, the contribution of high blood pressure to all-cause mortality should be higher in Japan than other countries. Thus, it should be important to know how many all-cause deaths are attributable to high blood pressure in different age groups. Our huge data set from 180 000 participants can be used to show the health consequence of high blood pressure in Japan. Each of our cohort studies was well administered and provided reliable data sets. The cohort studies were conducted all over Japan, confirming that our results are applicable to the general population in Japan.

Prospective studies collaboration showed that the relation of blood pressure to cardiovascular disease mortality was stronger in younger than in older subjects.[2] Recent studies in Japan showed that risk (all causes and cardiovascular disease) of high blood pressure in the Japanese population has increased.[21,28,29] The increasing trends in age-specific[28] and age-adjusted[29] hazard ratios were observed in nationwide cohort studies, and sex- and age- (aged 40 to 59 years and aged 60 to 79 years) specific hazard ratios showed increasing trends in the large-scale cohort study of the Ibaraki prefecture.[21] These studies raised the possibility that the association of blood pressure with all-cause mortality was stronger in the younger than in the older Japanese population. A data set from a huge population after fine age stratification could be used to prove findings that were never shown in Asian (Japanese) populations. We found significant interaction between age and blood pressure for all-cause mortality. This

Table 3. Multivariate Adjusted Hazard Ratio of All-Cause Mortality According to JNC-7 Classification, During Average 9.8 Years of Follow-Up

Sex	Age Category	Variable	Classification of Blood Pressure				PAF (%) (Reference: Normal)	PAF (%) (Reference: Normal+ Prehypertension
			Normal	Prehypertention	Hypertension (Stage 1)	Hypertension (Stage 2)		
Men	40 to 49	Total deaths	23	67	26	21	30.2	8.8
		Person-years	18 883	36 082	15 004	4899		
		Hazard ratio	1	1.45	1.28	3.38		
		95% CI		(0.89 to 2.38)	(0.70 to 2.34)	(1.76 to 6.50)		
	50 to 59	Total deaths	101	222	144	99	18.9	13.1
		Person-years	32 508	66 316	38 648	15 206		
		Hazard ratio	1	1.11	1.27	2.24		
		95% CI		(0.87 to 1.41)	(0.97 to 1.67)	(1.67 to 3.02)		
	60 to 69	Total deaths	198	691	644	367	25.7	11.3
		Person-years	28 313	79 508	69 671	30 000		
		Hazard ratio	1	1.26	1.39	1.82		
		95% CI		(1.07 to 1.48)	(1.18 to 1.64)	(1.52 to 2.18)		
	70 to 79	Total deaths	341	1194	1485	762	21.3	13.9
		Person-years	16 141	55 249	60 031	25 027		
		Hazard ratio	1	1.12	1.36	1.60		
		95% CI		(0.99 to 1.27)	(1.20 to 1.53)	(1.40 to 1.83)		
	80 to 89	Total deaths	182	660	844	497	10.5	7.0
		Person-years	2812	10 787	13 091	6082		
		Hazard ratio	1	1.05	1.11	1.31		
		95% CI		(0.88 to 1.25)	(0.93 to 1.31)	(1.09 to 1.57)		
Women	40 to 49	Total deaths	48	53	21	6	9.6	5.6
		Person-years	56 053	59 660	17 701	4817		
		Hazard ratio	1	1.09	1.42	1.44		
		95% CI		(0.73 to 1.62)	(0.83 to 2.45)	(0.60 to 3.45)		
	50 to 59	Total deaths	119	227	122	50	23.8	8.6
		Person-years	86 823	126 087	59 029	18 531		
		Hazard ratio	1	1.33	1.56	1.85		
		95% CI		(1.06 to 1.68)	(1.19 to 2.04)	(1.30 to 2.64)		
	60 to 69	Total deaths	204	513	435	240	22.3	13.8
		Person-years	66 277	146 391	108 093	36 453		
		Hazard ratio	1	1.16	1.35	2.13		
		95% CI		(0.98 to 1.37)	(1.14 to 1.62)	(1.74 to 2.60)		
	70 to 79	Total deaths	289	876	1037	506	11.8	13.3
		Person-years	28 708	91 539	91 441	33 945		
		Hazard ratio	1	0.98	1.20	1.48		
		95% CI		(0.85 to 1.12)	(1.05 to 1.38)	(1.27 to 1.72)		
	80 to 89	Total deaths	195	689	841	533	5.7	6.2
		Person-years	4702	17 815	21 342	10 758		
		Hazard ratio	1	0.99	1.07	1.17		
		95% CI		(0.84 to 1.18)	(0.90 to 1.27)	(0.98 to 1.40)		
Men and women combined	40 to 49	Total deaths	71	120	47	27	18.1	7.6
		Person-years	74 936	95 742	32 705	9716		
		Hazard ratio	1	1.22	1.28	2.48		
		95% CI		(0.90 to 1.65)	(0.86 to 1.91)	(1.53 to 4.04)		

(Continued)

Table 3. Continued

Sex	Age Category	Variable	Classification of Blood Pressure				PAF (%) (Reference: Normal)	PAF (%) (Reference: Normal+Prehypertension
			Normal	Prehypertention	Hypertension (Stage 1)	Hypertension (Stage 2)		
	50 to 59	Total deaths	220	449	266	149	22.1	11.3
		Person-years	119 331	192 403	97 677	33 737		
		Hazard ratio	1	1.22	1.42	2.15		
		95% CI		(1.03 to 1.45)	(1.17 to 1.72)	(1.72 to 2.69)		
	60 to 69	Total deaths	402	1204	1079	607	24.8	13.2
		Person-years	94 590	225 899	177 764	66 453		
		Hazard ratio	1	1.22	1.39	1.95		
		95% CI		(1.09 to 1.37)	(1.23 to 1.57)	(1.70 to 2.23)		
	70 to 79	Total deaths	630	2070	2522	1268	17.4	14.0
		Person-years	44 849	146 788	151 472	58 972		
		Hazard ratio	1	1.06	1.29	1.54		
		95% CI		(0.96 to 1.16)	(1.18 to 1.41)	(1.40 to 1.17)		
	80 to 89	Total deaths	377	1349	1685	1030	7.3	6.6
		Person-years	7513	28 602	34 433	16 840		
		Hazard ratio	1	1.01	1.08	1.22		
		95% CI		(0.90 to 1.15)	(0.96 to 1.22)	(1.08 to 1.39)		

Poisson regression models were used for estimating hazard ratio after adjusting for smoking, drinking, and body mass index. Classification of blood pressure status is according to JNC 7 guidelines (unit: mm Hg). Normal: SBP<120 and DBP<80; prehypertension: 120≤SBP<140 and 80≤DBP<90; hypertension (stage 1): 140≤SBP<160 and 90≤DBP<100; hypertension (stage 2): 160≤SBP and 100≤DBP, participants with hypertensive medication. Normal blood pressure level was set as the reference level. Population attributable fraction (PAF) was calculated in 2 ways. The reference level was set at (1) the normal blood pressure level and (2) below prehypertension (normal and prehypertension) level. Weighted averages of age-specific PAF, of which weights were person-years in each age category, were calculated as common PAFs. Common PAF was 22.7% in men, 17.9% in women, and 20.6 % in men and women combined (reference: normal) and 11.9% in men, 10.9% in women, and 11.9 % in men and women combined (reference: normal+prehypertension).

suggests that aggressive primary prevention of high blood pressure by all-cause mortality reduction benefits younger more than older people, although the absolute level of all-cause mortality was lower in younger than in older participants. As a consequence, absolute risk reduction should be lower in younger than in older people. Conversely, although the hazard ratio of high blood pressure was relatively lower in the elderly, absolute risk reduction should be higher in older than in younger people. Thus, the risk of hypertension should be age dependent. Because risk reduction is smaller in younger people, the high-risk approach might not be cost-effective. Therefore, the population approach is more suitable in younger than in older individuals. Conversely, for older individuals, the high-risk approach might be more beneficial.

The impact of lower blood pressure on the total mortality was determined by the population-attributable fraction. The study by Sairenchi et al[21] showed that the population-attributable fraction is ≈10% in men and 3% in women. In our study, the EPOCH-JAPAN estimated an age-specific population-attributable fraction for the contribution of blood pressure. In younger age ranges, a large number of deaths can be avoided by lowering blood pressure. This impact of blood pressure decreased with increasing age. When the prehypertension group was used for reference, the population-attributable fraction was ≈10% in each group. This proportion showed that lowering blood pressure is still effective even when all of the participants have prehypertension, which is a level of blood pressure that is achievable in practice.

We confirmed that all-cause mortality is consistently higher in individuals with prehypertension than in individuals with normal blood pressure. Thus, recommending lifestyle modification for them might reduce their all-cause mortality. However, because the absolute risk difference between normal blood pressure and prehypertension was not large, and population-attributable fraction was small, antihypertensive medication for them might not be recommended. Thus, we considered that the JNC-7 recommendation to modify lifestyle is the appropriate measure for prehypertension participants.

Hypertension is a leading cause of cardiovascular disease mortality and, thus, is a main contributor to total mortality. One of the advantages of selecting total mortality as an end point is that there is no misclassification issue in all-cause deaths compared with disease-specific ones. Although the interpretation of hypertension effect on total mortality was not intuitive, our examination of total mortality provided substantial information for public health purposes.

There were limitations in this study. First, the pooled data of most of the cohort studies were from baseline surveys performed during community health examinations. Participants in the cohort study volunteered to receive their health examinations, and for that reason their characteristics might be somewhat different from those of nonparticipants. This would influence the absolute measure of effect (mortality rate) and might underestimate the risk. However, these differences have little effect on relative measures of effect (such as hazard ratio). Thus, we considered that comparing

hazard ratios between age groups or population-attributable fractions might be largely unaffected. Second, we did not adjust for diabetes in this study. Because diabetes is an obesity-related risk factor for hypertension, we might have overestimated the risk posed by hypertension, per se. However, because prevalence of diabetes was very low during the baseline period in Japan, we believe that not adjusting for diabetes should have no substantial effect on our result.

In conclusion, high blood pressure raised the risk of total mortality, and this increase was higher relatively, but not absolutely, in younger than in older individuals. A relatively large amount of the population-attributable fraction was observed in the younger age group. Blood pressure management is an important preventive measure for the Japanese population regardless of age.

Perspectives

The present study showed the relation between blood pressure and total mortality in the Japanese population in detail. The results showed that apparent relation between blood pressure and total mortality was present not only in the elderly but also in a younger age group for both men and women. The result encourages us that blood pressure management was an important preventive measure for Japanese participants regardless of age. Furthermore, the people with prehypertension showed high hazard ratios in most age groups. This detailed information would provide effective public health policy and clinical practice not only in the Japanese but also in the Asian population.

Appendix

Evidence for Cardiovascular Prevention From Observational Cohorts in Japan Research Group is composed of the following individuals: chairperson: Hirotsugu Ueshima (Shiga University of Medical Science); writing committee: Yoshitaka Murakami, Atsushi Hozawa, Tomonori Okamura, and Hirotsugu Ueshima; statistical analysis: Yoshitaka Murakami; secretariat: Yoshitaka Murakami; and the executive committee: Hirotsugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Medicine), Hiroyasu Iso (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Kazunori Kodama (Radiation Effects Research Foundation), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (National Cardiovascular Center), Akira Okayama (Japan Anti-Tuberculosis Association), Shigeyuki Saitoh (Sapporo Medical University), Akiko Tamakoshi (National Center for Geriatrics and Gerontology), Ichiro Tsuji (Tohoku University Graduate School of Medicine), and Yoko Izumi (Ibaraki Prefecture).

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Disclosures

None.

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Alcohol Consumption and Mortality From Stroke and Coronary Heart Disease Among Japanese Men and Women

The Japan Collaborative Cohort Study

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Background and Purpose—Previous studies have demonstrated the association between alcohol consumption and cardiovascular mortality. However, the sex-specific association between alcohol consumption and mortality from stroke and coronary heart disease remains unclear.

Methods—Between 1988 and 1990, 34 776 men and 48 906 women aged 40 to 79 years completed a self-administered questionnaire including information about alcohol consumption. They were followed-up for a median duration of 14.2 years.

Results—Of the 83 682 respondents, 1628 died from stroke and 736 died from coronary heart disease. For men, heavy drinking (≥46.0 g ethanol/day) was associated with increased mortality from total, hemorrhagic, and ischemic strokes, whereas light-to-moderate drinking was associated with reduced mortality from total cardiovascular disease, compared with not drinking. The respective multivariable hazard ratios (95% CI) were 1.48 (1.22 to 1.80) for total stoke, 1.67 (1.17 to 2.38) for hemorrhagic stroke, 1.35 (1.04 to 1.75) for ischemic stroke, and 0.88 (0.78 to 1.00) for total cardiovascular disease. Women who were heavy drinkers (≥46.0 g ethanol/day) showed increased mortality from coronary heart disease, and there was reduced mortality from total cardiovascular disease for drinkers of 0.1 to 22.9 g ethanol per day compared with mortality for nondrinkers. The respective multivariable hazard ratios (95% CI) for the 2 categories of drinkers were 4.10 (1.63 to 10.3) and 0.75 (0.62 to 0.91).

Conclusions—Heavy alcohol consumption is associated with increased mortality from total stroke, particularly hemorrhagic stroke, and total cardiovascular disease for men, and from coronary heart disease for women, whereas light-to-moderate drinking may be associated with reduced mortality from cardiovascular disease for both sexes. **(*Stroke*. 2008;39:2936-2942.)**

Key Words: alcohol consumption ■ coronary heart disease ■ mortality ■ stroke

The large number of cohort studies showed an increased risk of hemorrhagic stroke among male heavy drinkers,[1–10] and reduced risk of ischemic stroke[9–11] and coronary heart disease[12–17] among male light-to-moderate drinkers.

A few studies have reported the association between moderate-to-heavy alcohol consumption and increased risk of hemorrhagic stroke,[5,18] and light-to-moderate alcohol consumption was associated with reduced risk of cardiovascular disease for women.[18–20] A cohort study for a US prepaid health care program found that women consuming ≥6 drinks per day showed a nonsignificant excess risk for hemorrhagic stroke.[5] The Nurses' Health Study showed that light-to-moderate alcohol consumption was associated with reduced incidence of ischemic stroke and coronary heart disease[18] and reduced mortality from cardiovascular disease,[19] compared with incidence of ischemic stroke and coronary heart disease in those who do not drink. A Swedish cohort study[20] also reported that light alcohol consumption among women was

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associated with reduced incidence of and morality from ischemic stroke. However, no such evidence is available for women in Asian countries, probably because of the low prevalence of drinkers and coronary heart disease. To examine the sex-specific associations of alcohol consumption with mortality from total stroke, stroke subtypes, and coronary heart disease, we analyzed data from a large prospective study of ≈83 000 Japanese men and women.

Materials and Methods

Study Cohort

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho was conducted from 1988 to 1990, when 110 792 subjects (46 465 men and 64 327 women) aged 40 to 79 years and living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires concerning their lifestyles and medical histories of previous cardiovascular disease and cancer at baseline. The details of the study procedure have been described previously.[21] In most communities, informed consent was obtained individually from members of the cohort, whereas in several communities, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders and mayors. Follow-up surveys were conducted annually to verify the vital status of the participants. Among the 110 792 cohort participants, we excluded the 22 358 subjects (9579 men and 12 779 women) who had missing information on drinking habits such as drinking status, the frequency of drinking, and the amount of alcohol consumed, and 4752 subjects (2110 men and 2642 women) who reported a history of cancer, stroke, or myocardial infarction. A total of 34 776 men and 48 906 women were included in the study.

Mortality Surveillance

For mortality surveillance in each of the communities, 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 then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics from 1988 to 1994 according to the *International Classification of Diseases*, 9th revision (ICD-9), and from 1995 to 2003 according to the 10th revision (ICD-10). Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subjects were treated as censored cases. Cause-specific mortality was determined separately in terms of total cardiovascular disease (ICD-9 codes 390 to 459, ICD-10 codes I01 to I99), total coronary heart disease (codes 410 to 414 and I20 to I25), and total stroke (430 to 438 and I60 to I69). The latter category was further subdivided into intraparenchymal hemorrhage (431 and I61), subarachnoid hemorrhage (430 and I60), and ischemic stroke (433 to 434 and I63 and I693). The follow-up is believed to be complete by systematic examination of death certificates and residency status. By December 31, 2003, 12 100 subjects were treated as censored when they died, and 3532 subjects were treated as censored when they moved out of the study area. The median follow-up period for the participants was 14.2 years. This study was approved by the Ethics Committee of the Nagoya University School of Medicine.

Baseline Survey

The baseline data were collected with a self-administered questionnaire including information about alcohol consumption, demographic characteristics, histories of hypertension, diabetes mellitus, and other chronic diseases, and habits related to smoking, diet, and exercise. Alcohol drinking status was established by asking the subjects whether they were nondrinkers, ex-drinkers, or current drinkers. Ex-drinkers and current drinkers were also asked about the age at which they started drinking, frequency of alcohol intake per week during the previous year (less than once/week, 1 to 2 times/week, 3 to 4 times/week, and almost every day), type of beverage (sake [rice wine], shochu [a type of brandy], beer, whiskey, or wine), and the amount consumed per occasion. The unit of amount consumed per occasion was "gou", which is the equivalent of ≈23 g of alcohol. The amount of ethanol per day was calculated as follows: the unit of amount consumed per occasion multiplied by the frequency of alcohol consumption per week divided by 7. The validity of the alcohol questionnaire was examined by serum γ-glutamyl transferase among the subsample participants who underwent the baseline health check-ups (4969 men and 9732 women). The age-adjusted mean values of serum γ-glutamyl transferase according to the alcohol consumption categories (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, 46.0 to 68.9 g/day, and ≥69.0 g/day for men, and nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, and ≥46.0 g/day for women) were 20, 26, 27, 37, 51, and 68 IU/L, respectively, for men and 15, 18, 17, 25, and 48 IU/L, respectively, for women. The reproducibility and validity for dietary intakes of fish, vegetables, and fruit were reported elsewhere.[22]

Statistical Analysis

Statistical analyses were based on sex-specific rates for mortality from stroke during the follow-up periods from 1988 and from 1990 to 2003. The follow-up person-years were calculated from the date of completing the baseline questionnaire to death, moving out of the community, or the end of 2003, whichever was first. We classified alcohol consumption into 6 categories for men (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, 46.0 to 68.9 g/day, and ≥69.0 g/day) and into 5 categories for women (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, and ≥46.0 g/day). Sex-specific age-adjusted mean values and prevalence of cardiovascular risk factors were calculated. We conducted tests for linear trends of covariates by using the median values of alcohol consumption categories. The sex-specific hazard ratios with 95% CI for mortality from stroke and coronary heart disease were then calculated with reference to the risk for nondrinkers. These estimates were adjusted for age and other potential confounding factors by using the Cox proportional hazards model. Potential confounding factors for the adjustment were baseline of age, smoking status (never, ex-smoker, current smokers of 1 to 19, and ≥20 cigarettes/day), BMI (sex-specific quintiles), history of hypertension, history of diabetes, frequency of exercise (<1, 1 to 2, 3 to 4, and ≥5 hours/week), perceived mental stress (low, moderate, high), education level (primary school, junior high school, high school, college or higher), vegetable intake (sex-specific quintiles), and fish and fruits intake (almost never, 1 to 2 times/month, 1 to 2 times/week, 3 to 4 times/week, and almost every day). SAS (version 8.02) was used for all statistical analyses.

Results

After completion of the follow-up of 1 065 295 person-years, the deaths of 1628 subjects from stroke (864 men and 764 women) and of 736 from coronary heart disease (431 men and 305 women) had been documented. The sex-specific mortality per 1000 person-year among men was 2.0 for stroke and 1.0 for coronary heart disease, and the respective mortality among women was 1.2 and 0.5. The deaths for men included 202 intraparenchymal hemorrhages, 74 subarachnoid hemorrhages, 507 ischemic strokes, and 431 coronary heart diseases. For women, the corresponding numbers were 151, 157, 388, and 305. Table 1 shows sex-specific age-adjusted mean values or prevalence of risk characteristics at baseline by category of alcohol consumption. The respective proportions of nondrinkers, ex-drinkers, and current drinkers were 22%, 7%, and 71% for men, and 83%, 2%, and 15% for women.

Table 1. Age-Adjusted Mean Values or Prevalence (%) of Risk Characteristics at Baseline by Alcohol Consumption Category for Men and Women

			Ethanol Intake, g/day				
	Nondrinkers	Ex-Drinkers	0.1–22.9	23.0–45.9	46.0–68.9	≥69.0	*P* for Trend
Men	7821	2378	6130	8056	7067	3324	
Age, yr	59	62	56	57	55	54	<0.001
Mean BMI, kg/m^2	22.6	22.4	22.7	22.6	22.7	22.7	<0.001
History of hypertension, %	13	20	17	20	22	22	<0.001
History of diabetes, %	5	11	6	6	5	6	0.002
Current smokers, %	49	46	45	50	58	65	<0.001
College or higher education, %	12	13	18	15	13	10	<0.001
Exercise ≥5 hours/wk, %	5	5	6	7	7	7	<0.001
High level of stress, %	23	27	24	22	21	24	0.03
Vegetable intake, times/wk	27.4	28.1	27.4	27.9	27.4	26.6	0.03
Fish intake, times/wk	6.3	6.6	6.5	7.0	7.5	8.0	<0.001
Fruit intake, times/wk	7.2	6.9	6.7	6.7	6.0	5.6	<0.001
Women	40 826	884	5848	1020	328		
Age, yr	57	58	55	55	53		<0.001
Mean BMI, kg/m^2	22.9	23.0	22.9	22.9	23.4		0.04
History of hypertension, %	21	24	19	24	27		0.001
History of diabetes, %	3	8	3	3	3		0.05
Current smokers, %	3	19	7	20	38		<0.001
College or higher education, %	8	7	10	7	7		0.37
Exercise ≥5 hours/wk, %	3	5	6	6	5		<0.001
High level of stress, %	19	28	22	23	22		0.001
Vegetable intake, times/wk	32.4	30.3	31.9	31.0	29.0		<0.001
Fish intake, times/wk	7.1	6.8	7.1	7.3	7.5		0.03
Fruit intake, times /wk	8.6	8.3	8.5	7.7	6.5		<0.001

Compared with nondrinkers, moderate-to-heavy drinkers, both men and women, tended to be younger, more hypertensive, heavier smokers, and had the higher frequency of fish intake and the lower frequency of fruit intake. Tables 2 and 3 show age-adjusted and multivariable-adjusted hazard ratios for total stroke, stroke subtypes, coronary heart disease, and ischemic and total cardiovascular disease for men and women. For women, the data on intraparenchymal and subarachnoid hemorrhage were collapsed as hemorrhagic stroke because of the limited number of deaths. Increases in the risks of mortality from total and hemorrhagic strokes were observed among male consumers of 46.0 to 68.9 and ≥69.0 g ethanol per day. Heavy drinking of ≥69.0 g ethanol per day was also associated with increased risk of mortality from total stroke and total cardiovascular disease among men. Male ex-drinkers showed higher risks of mortality from total stroke, particularly hemorrhagic stroke, either intraparenchymal or subarachnoid hemorrhage, and total cardiovascular disease. Light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with a reduced risk of mortality from total cardiovascular disease among men.

For women, there was an excess risk of mortality from coronary heart disease among drinkers of ≥46.0 g ethanol per day compared with nondrinkers, and a reduced risk of mortality from cardiovascular disease among drinkers of 0.1 to 22.9 g ethanol per day. The multivariable hazard ratio (95% CI) of mortality for moderate-to-heavy drinkers compared with nondrinkers was 4.10 (1.63 to 10.3) for coronary heart disease and 3.29 (1.61 to 6.73) for ischemic cardiovascular disease, whereas that for light drinkers compared with nondrinkers was 0.74 (0.60 to 0.91) for total cardiovascular disease.

Discussion

In the large prospective study of Japanese men and women whose stroke mortality was more than double that of coronary heart disease, we found that heavy alcohol consumption of ≥69.0 g ethanol per day was associated with increased risk of mortality from hemorrhagic stroke among men, whereas light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with reduced mortality from ischemic cardiovascular disease among men. For women, light drinking of 0.1 to 22.9 g ethanol per day showed an association with reduced mortality from ischemic cardiovascular disease.

The excess mortality from hemorrhagic stroke associated with heavy alcohol consumption and the reduced mortality from ischemic cardiovascular disease associated with light-to-moderate alcohol consumption are consistent with the results from previous studies of whites and Japanese with

Table 2. HR and 95% CI of Mortality from Total Stroke, Coronary Heart Disease, and Total Cardiovascular Disease by Alcohol Consumption Category for Men

			Ethanol Intake, g/day			
	Nondrinkers	Ex-Drinkers	0.1–22.9	23.0–45.9	46.0–68.9	≥69.0
Person-years	96 423	25 919	78 478	101 256	90 000	41 588
Total stroke						
N	200	126	114	168	173	83
Age-adjusted HR	1.00	1.93 (1.55–2.42)	0.91 (0.72–1.15)	0.98 (0.80–1.21)	1.46 (1.19–1.79)	1.89 (1.46–2.46)
Multivariable HR*	1.00	1.90 (1.52–2.39)	0.95 (0.75–1.20)	0.96 (0.78–1.19)	1.39 (1.12–1.73)	1.71 (1.31–2.24)
Multivariable HR†			0.96 (0.79–1.15)		1.48 (1.22–1.80)	
Hemorrhagic stroke						
N	55	31	41	52	60	37
Age-adjusted HR	1.00	1.80 (1.16–2.80)	1.09 (0.72–1.63)	1.02 (0.70–1.49)	1.51 (1.05–2.19)	2.30 (1.51–3.51)
Multivariable HR*	1.00	1.79 (1.15–2.80)	1.16 (0.76–1.76)	1.02 (0.69–1.51)	1.47 (1.00–2.16)	2.16 (1.39–3.35)
Multivariable HR†			1.08 (0.76–1.53)		1.67 (1.17–2.38)	
Intraparenchymal hemorrhage						
N	41	26	30	39	44	22
Age-adjusted HR	1.00	2.00 (1.22–3.27)	1.09 (0.68–1.75)	1.05 (0.67–1.62)	1.56 (1.02–2.40)	1.98 (1.17–3.35)
Multivariable HR*	1.00	2.00 (1.22–3.30)	1.16 (0.71–1.88)	1.05 (0.67–1.64)	1.52 (0.97–2.38)	1.87 (1.09–3.22)
Multivariable HR†			1.09 (0.73–1.63)		1.62 (1.07–2.45)	
Subarachnoid hemorrhage						
N	14	5	11	13	16	15
Age-adjusted HR	1.00	1.21 (0.44–3.38)	1.07 (0.48–2.36)	0.95 (0.45–2.02)	1.41 (0.68–2.90)	3.05 (1.45–6.39)
Multivariable HR*	1.00	1.16 (0.41–3.26)	1.16 (0.51–2.63)	0.96 (0.44–2.12)	1.38 (0.65–2.96)	2.81 (1.29–6.12)
Multivariable HR†			1.05 (0.52–2.09)		1.83 (0.93–3.61)	
Ischemic stroke						
N	126	88	60	101	95	37
Age-adjusted HR	1.00	2.12 (1.62–2.79)	0.80 (0.59–1.09)	0.99 (0.76–1.28)	1.44 (1.10–1.88)	1.60 (1.10–2.31)
Multivariable HR*	1.00	2.11 (1.59–2.78)	0.81 (0.59–1.11)	0.94 (0.72–1.24)	1.34 (1.01–1.77)	1.39 (0.95–2.04)
Multivariable HR†			0.89 (0.70–1.13)		1.35 (1.04–1.75)	
Coronary heart disease						
N	116	56	71	90	65	33
Age-adjusted HR	1.00	1.50 (1.09–2.07)	0.94 (0.70–1.27)	0.88 (0.66–1.15)	0.87 (0.64–1.18)	1.16 (0.78–1.71)
Multivariable HR*	1.00	1.35 (0.97–1.86)	0.96 (0.71–1.30)	0.82 (0.62–1.09)	0.76 (0.55–1.04)	0.95 (0.64–1.41)
Multivariable HR†	1.00		0.88 (0.69–1.13)		0.81 (0.61–1.08)	
Ischemic cardiovascular disease						
N	242	144	131	191	160	70
Age-adjusted HR	1.00	1.82 (1.48–2.24)	0.87 (0.71–1.08)	0.93 (0.77–1.13)	1.14 (0.93–1.40)	1.37 (1.04–1.79)
Multivariable HR*	1.00	1.71 (1.39–2.12)	0.89 (0.72–1.11)	0.88 (0.73–1.08)	1.03 (0.84–1.27)	1.16 (0.88–1.53)
Multivariable HR†			0.89 (0.75–1.05)		1.07 (0.88–1.29)	
Total cardiovascular disease						
N	487	282	269	379	342	162
Age-adjusted HR	1.00	1.77 (1.53–2.06)	0.88 (0.76–1.02)	0.90 (0.79–1.03)	1.16 (1.01–1.33)	1.47 (1.23–1.76)
Multivariable HR*	1.00	1.66 (1.43–1.93)	0.90 (0.77–1.05)	0.87 (0.76–1.00)	1.07 (0.92–1.23)	1.28 (1.07–1.55)
Multivariable HR†			0.88 (0.78–1.00)		1.13 (0.99–1.29)	

*Adjusted for age, smoking status, BMI, history of hypertension, history of diabetes, frequency of exercise, perceived mental stress, education level, and intake of vegetables, fish, and fruit.

†Calculated for drinkers of 0.1 to 45.9 g ethanol per week and those of ≥46.0 g ethanol per week.

HR indicates hazard ratio.

regard to hemorrhagic stroke,[1–10] ischemic stroke,[9–11] and coronary heart disease.[12–17]

The excess mortality of hemorrhagic stroke may be partly influenced by alcohol-induced high blood pressure.[23] Alcohol also leads to reduced platelet aggregation[24] and enhanced fibrinolysis through increased secretion of plasminogen activators from endothelial cells.[25] Moreover, the possible mechanisms by which light alcohol consumption may lead to reduced mortality of ischemic cardiovascular disease have been identified as elevated concentration of HDL cholesterol,[26]

Table 3. HR and 95% CI of Mortality from Total Stroke, Coronary Heart Disease, and Total Cardiovascular Disease by Alcohol Consumption Category for Women

			Ethanol Intake (g/day)		
	Nondrinkers	Ex-Drinkers	0.1–22.9	23.0–45.9	≥46.0
Person-years	529 265	10 712	74 702	12 872	4082
Total stroke					
N	684	14	53	7	6
Age-adjusted HR	1.00	1.00 (0.59–1.70)	0.83 (0.63–1.10)	0.59 (0.28–1.24)	2.33 (1.04–5.20)
Multivariable HR*	1.00	0.87 (0.51–1.48)	0.87 (0.65–1.15)	0.59 (0.28–1.24)	1.92 (0.85–4.35)
Multivariable HR†			0.82 (0.63–1.08)		
Hemorrhagic stroke					
N	272	6	24	3	3
Age-adjusted HR	1.00	1.08 (0.48–2.43)	0.83 (0.55–1.27)	0.58 (0.19–1.82)	2.32 (0.74–7.26)
Multivariable HR*	1.00	0.95 (0.42–2.17)	0.84 (0.55–1.29)	0.52 (0.17–1.64)	1.61 (0.50–5.19)
Multivariable HR†			0.79 (0.53–1.18)		
Ischemic stroke					
N	353	8	22	2	3
Age-adjusted HR	1.00	1.10 (0.55–2.22)	0.74 (0.48–1.13)	0.34 (0.09–1.37)	2.75 (0.88–8.57)
Multivariable HR*	1.00	0.87 (0.42–1.78)	0.78 (0.51–1.21)	0.36 (0.09–1.44)	2.43 (0.77–7.69)
Multivariable HR†			0.71 (0.47–1.09)		
Coronary heart disease					
N	267	6	20	7	5
Age-adjusted HR	1.00	1.10 (0.49–2.47)	0.84 (0.54–1.33)	1.53 (0.72–3.25)	5.44 (2.24–13.2)
Multivariable HR*	1.00	0.85 (0.38–1.94)	0.83 (0.53–1.33)	1.45 (0.68–3.11)	4.10 (1.63–10.3)
Multivariable HR†			0.94 (0.62–1.41)		
Ischemic cardiovascular disease					
N	620	14	42	9	8
Age-adjusted HR	1.00	1.10 (0.65–1.87)	0.78 (0.57–1.07)	0.86 (0.45–1.66)	3.98 (1.98–8.00)
Multivariable HR*	1.00	0.86 (0.50–1.48)	0.81 (0.59–1.11)	0.87 (0.45–1.68)	3.29 (1.61–6.73)
Multivariable HR†			0.82 (0.61–1.09)		
Total cardiovascular disease					
N	1494	30	99	22	12
Age-adjusted HR	1.00	0.98 (0.68–1.41)	0.72 (0.59–0.89)	0.85 (0.56–1.29)	2.19 (1.24–3.88)
Multivariable HR*	1.00	0.82 (0.57–1.18)	0.74 (0.60–0.91)	0.81 (0.53–1.24)	1.73 (0.97–3.08)
Multivariable HR†			0.75 (0.62–0.91)		

*Adjusted for age, smoking status, body mass index, history of hypertension, history of diabetes, frequency of exercise, perceived mental stress, education level, and intake of vegetables, fish, and fruit.

†Calculated for drinkers of 0.1 to 45.9 g ethanol per week.

reduced platelet aggregation,[24] enhanced fibrinolysis,[25] and reduced plasma fibrinogen levels.[27]

Our study demonstrated a reduced mortality from ischemic cardiovascular disease associated with light drinking of 0.1 to 22.9 g ethanol per day among Japanese women. Our finding is consistent with that of the Nurse's Health study, which reported that light-to-moderate drinking of 1.5 to 29.9 g ethanol per day was associated with a similarly reduced morality from coronary heart disease and cardiovascular disease.[19] Furthermore, in the Swedish cohort study,[20] an average consumption of 0 to 5 g ethanol per day by women was associated with reduced morality from ischemic stroke, but such an association was not found for men. The multivariable hazard ratio of morality from ischemic stroke was 0.6 (0.5 to 0.8) for women and 1.3 (0.9 to 2.0) for men compared with that for never-drinkers.

We detected an excess risk of mortality from coronary heart disease associated with drinkers of ≥46.0 g ethanol per day among women, albeit the number of deaths in heavy drinkers was small, but such an excess risk was not found among men (P for interaction=0.001). Heavy alcohol consumption enhances the probability of both atrial and life-threatening ventricular arrhythmias and atrioventricular block through the destabilization of potassium and magnesium metabolism and the stimulation of catecholamine.[28,29] Further, women have lower alcohol dehydrogenase activity in the liver than men,[30] so that women have higher blood alcohol concentrations than men after ingestion of the same dose of

alcohol, even when the dose is adjusted for body weight.[31] The Nurse's Health study[19] did not find the excess mortality, but the number of deaths among heavy drinkers of ≥30g ethanol per day in that cohort was also small (n=9). Further research is needed to understand the health consequences of heavy drinking in females.

Our study also showed an excess risk of mortality from total stroke, either hemorrhagic or ischemic stroke, among male ex-drinkers. The 8424 current drinkers at baseline who also responded to the 5-year follow-up comprised 285 ex-drinkers and 8139 continuing drinkers. The ex-drinkers may have stopped because of ill health, because the prevalence of a history of diabetes, liver disease, gallstone or gallbladder disease, gastric or duodenal ulcer, and tuberculosis at baseline was much higher for quitters than continuing drinkers. However, the prevalence of history of those diseases did not differ for female ex-drinkers and continuing drinkers.

The strengths of our study are its prospective design and the high statistical power for the detection of sex-specific associations of a wide range of alcohol consumption with mortality from total stroke, coronary heart disease, and total cardiovascular disease. Our findings for women are noteworthy because the evidence has been largely limited for Asian women.

The limitations of our study also need to be discussed. First, drinkers may consume different amounts of alcohol during occasional and weekend drinking. However, we could not estimate alcohol consumption resulting from binge drinking because the questionnaire did not ask this information. It has been suggested that binge drinking increases the risk of myocardial infarction.[32] However, it can be assumed that binge drinking was not common for our study subjects, because 98% to 99% of heavy drinkers of ≥46.0 g ethanol per day reported consuming alcohol beverages almost every day. Second, we estimated alcohol consumption by the single self-administrated questionnaire, which would be liable to misclassification. However, there was a moderate correlation between alcohol consumption and serum γ-glutamyl transferase, a marker of alcohol intake, for both sexes. The data on alcohol consumption in a 5-year follow-up survey were available from only 25 of the 45 communities. However, when we examined the subsample participants (10 214 men and 15 379 women) who completed the alcohol questionnaire at baseline and the followed-up surveys, we found that the proportions of the same category, the adjacent category, and the reversal category of alcohol consumption were 59%, 83%, and 0.08%, respectively, for men, and 90%, 91%, and 0.06%, respectively, for women. Third, we used the mortality data as endpoints rather than incidence data, which may lead to misclassification in the diagnosis of stroke, stroke subtypes, and coronary heart disease. The widespread use of computer tomography in local hospitals since the 1980s has probably made the diagnosis of stroke and its subtypes reported on the death certificates sufficiently accurate.[33] For coronary heart disease, however, approximately one-fourth of ischemic heart disease deaths appearing on death certificates were misdiagnosed according to the validation studies.[34,35] Finally, although hazard ratios were adjusted for selected cardiovascular risk factors and social factors, we cannot exclude the possibility that other risk factors such as socioeconomic status and psychosocial factors may have affected our findings.

Conclusion

In conclusion, the results of our study of a large cohort of Japanese men and women indicate that heavy alcohol consumption is associated with increased mortality from total stroke, particularly hemorrhagic stroke, and total cardiovascular disease for men, and with increased mortality from coronary heart disease for women. Also, light-to-moderate alcohol consumption may be associated with reduced mortality from cardiovascular disease for both men and women.

Appendix

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Disclosure

None.

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Fish, ω-3 Polyunsaturated Fatty Acids, and Mortality From Cardiovascular Diseases in a Nationwide Community-Based Cohort of Japanese Men and Women

The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study

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Objectives The objective of our study was to test the hypothesis that fish or ω-3 polyunsaturated fatty acids (PUFA) intakes would be inversely associated with risks of mortality from ischemic heart disease, cardiac arrest, heart failure, stroke, and total cardiovascular disease.

Background Data on associations of dietary intake of fish and of ω-3 PUFA with risk of cardiovascular disease among Asian societies have been limited.

Methods We conducted a prospective study consisting of 57,972 Japanese men and women. Dietary intakes of fish and ω-3 PUFA were determined by food frequency questionnaire, and participants were followed up for 12.7 years. Hazard ratios and 95% confidence intervals were calculated according to quintiles of fish or ω-3 PUFA intake.

Results We observed generally inverse associations of fish and ω-3 PUFA intakes with risks of mortality from heart failure (multivariable hazard ratio [95% confidence interval] for highest versus lowest quintiles = 0.76 [0.53 to 1.09] for fish and 0.58 [0.36 to 0.93] for ω-3 PUFA). Associations with ischemic heart disease or myocardial infarction were relatively weak and not statistically significant after adjustment for potential risk factors. Neither fish nor ω-3 PUFA dietary intake was associated with mortality from total stroke, its subtypes, or cardiac arrest. For mortality from total cardiovascular disease, intakes of fish and ω-3 PUFA were associated with 18% to 19% lower risk.

Conclusions We found an inverse association between fish and ω-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure, suggesting a protective effect of fish intake on cardiovascular diseases. (J Am Coll Cardiol 2008;52:988–96) © 2008 by the American College of Cardiology Foundation

Inverse associations of dietary intake of fish and ω-3 polyunsaturated fatty acids (PUFA) with the risk of ischemic heart disease (IHD) have been well described mainly in Western populations (1), but the data on Asian societies have been limited. There have been only 3 cohort studies in China (2) and Japan (3,4), and a recent randomized con-

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trolled trial among hypercholesterolemic patients in Japan (5). The evidence for an association between fish intake and the risk of stroke has also been limited, although a protective effect was suggested from a meta-analysis (6). Further, it is possible that dietary intakes of fish and ω-3 PUFA may reduce the risk of heart failure (7), but the data on this issue are quite limited (8,9).

Several mechanisms, including antiarrhythmic effects, modulation of autonomic function, decreased platelet aggregation, and vasodilation, have been suggested for the association between fish or ω-3 PUFA and risk of cardiovascular disease (10). From an epidemiological standpoint, it is important to replicate the results in different populations and confirm the associations with large representative data. The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study is a nationwide, community-based follow-up study of cardiovascular disease with one of the largest number of subjects in Asia, including many cases of heart failure, which has not been examined in Asia. Thus, we used these data to examine the associations of dietary intakes of fish and ω-3 PUFA with the risk of mortality from cardiovascular disease in Japan, where average fish intake is high compared with that of Western countries—approximately 3 to 4 times more among Japanese than among white Americans (11). Our a priori hypothesis was that the dietary intakes of fish and ω-3 PUFA would be associated with reduced risk of mortality from IHD, cardiac arrest, heart failure, stroke, and total cardiovascular disease in this population with high fish intake.

Methods

Study cohort. The JACC study comprised a nationwide community-based sample of 110,792 persons (46,465 men and 64,327 women) from 45 administrative districts of Japan. Participants were 40 to 79 years of age during the baseline period (1988 to 1990) and completed self-administered questionnaires concerning their life-styles and medical histories of previous cardiovascular disease or cancer (12). We excluded persons who reported a history of heart disease (IHD, arrhythmia, heart failure, or unspecified heart disease), stroke, or cancer at the baseline survey, or those missing the fresh fish item, with more than 1 item missing from the other 3 fish items, or with more than 4 missing items from the 33 items on the dietary questionnaire. As a result, we included 22,881 men and 35,091 women from 34 communities with complete information on their dietary information. Written or explicitly verbal informed consent was obtained before participants completed the questionnaire. In several communities, the informed consent was obtained from community leaders instead of individual participants, which had been in common practice for informed consent in Japan at that time. The JACC study protocol was approved by the Medical Ethical Committees of the Nagoya University School of Medicine.

Abbreviations and Acronyms

CI = confidence interval
HR = hazard ratio
IHD = ischemic heart disease
PUFA = polyunsaturated fatty acids

Mortality surveillance. In each community, investigators conducted a systematic review of death certificates. In Japan, registration of death is legally required and is believed to be followed across Japan. Thus, all deaths that occurred in the cohort were ascertained by 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 censored. The date of moving from the community was verified by population-register sheets. In the present study, the follow-up was conducted through the end of 2003, except for 2 communities in which the follow-up had ended in 1999. The average follow-up period for the participants was 12.7 years. We used the underlying cause of death coded by the International Statistical Classification of Diseases and Related Health Problems-10th Revision (ICD-10) to identify mortality end points: I60 to I69 for stroke, I60 for subarachnoid hemorrhage, I61 for intraparenchymal hemorrhage, I63 for ischemic stroke, I20 to I25 for IHD, I21 for myocardial infarction, I46 for cardiac arrest, I47 to I49 for arrhythmic death, I50 for heart failure, and I00 to I99 for total cardiovascular disease. Because of the small number of cases, we pooled cardiac arrest and other arrhythmic death as "cardiac arrest."

Intakes of fish and ω-3 PUFA. The food frequency questionnaire included 33 foods, including 4 fish items: fresh fish, *kamaboko* (steamed fish paste), dried or salted fish, and deep-fried foods or *tempura* (a common form of deep-fried fish or shellfish). Five choices were presented for each item: rarely, 1 to 2 days a month, 1 to 2 days a week, 3 to 4 days a week, and almost every day; these choices were converted to scores of 0, 0.05 (1.5 of 30), 0.214 (1.5 of 7), 0.5 (3.5 of 7), and 1, respectively. The portion size was estimated by a previous validation study (13) described in the following text, and assigned as 63 g for fresh fish, 20 g for steamed fish paste, 29 g for dried or salted fish, and 29 g for deep-fried fish, which was estimated as 26% of 113 g for deep-fried foods or *tempura* calculated by dietary records of the validation study. The consumption of fish (g/day) was calculated by multiplying the frequency scores and portion sizes, and summing across the 4 items. For missing data on either dried or salted fish, deep-fried fish, or steamed fish paste (n = 5,300), we assigned the median consumption values in the total sample.

The previous validation study also provided the values for nutrient and fatty acid intake, based on the Japan Food Table-4th Version. The values of ω-3 PUFA (including non–long-chain ω-3 PUFA) assigned for 1 portion were, for example, 1.009 g for fresh fish, 0.042 g for steamed fish