(3) ベースライン時の血圧レベルとその後 24 年間の循環器疾患死亡リスクとの関連 : NIPPON DATA80

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背景：欧米では、ベースライン時の血圧がその後 20 年以上の長期間にわたって循環器疾患死亡を予測することが報告されているが、脳卒中が多いアジアにおいてはほとんどエビデンスはない。そこで、日本人を代表する集団でベースライン時の血圧がその後、24 年間の循環器疾患死亡を予測するかについて検討した。

方法：循環器疾患の既往がなく、降圧薬の治療を受けていない 30 歳以上の日本人男女 8592 名を対象として 24 年間追跡を行った。血圧カテゴリは JNC7 分類に従った。正常血圧をリファレンスしてハザード比は Cox 比例ハザードモデルを用いてその他の交絡要因を調整して求めた。

結果：観察期間中に 689 名が循環器疾患で死亡した（うち脳卒中は 321 名）。循環器疾患死亡の調整済みハザード比は前高血圧から順に有意な上昇を認めた。血圧の人口寄与危険割合（PAF）は全循環器疾患死亡で 43％、脳卒中死亡では 48％であった。高齢者（60 歳以上）と比較して若年者(30 歳から 59 歳)のハザード比及び PAF は高かった。若年者では血圧の PAF は全循環器疾患死亡では 81％を占めた。さらに降圧薬治療者を含めた追加解析では、降圧薬治療者のハザード比が他の血圧カテゴリより高値であった。

結論：正常血圧より高い血圧はその後、24 年間の循環器疾患死亡に影響を与えた。若年者における血圧上昇は循環器疾患死亡に長期にわたって影響を及ぼすことは若い世代から血圧の上昇に対する一次予防の重要性を示唆している。

Original Article

Long-term risk of BP values above normal for cardiovascular mortality: a 24-year observation of Japanese aged 30 to 92 years

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Objective: In Western populations, blood pressure (BP) measured at baseline has been reported to predict long-term (over 20 years) risk of mortality from cardiovascular diseases (CVDs). However, corresponding evidence is scarce in Asia where stroke is dominant. We investigated the association between baseline BP and 24-year mortality risk due to CVD, in a representative Japanese general population.

Methods: We followed up a nationwide sample of 8592 Japanese, aged 30 years or above without a history of CVD and antihypertensive medication at baseline, for 24 years. Hazard ratios for CVD mortality in BP categories defined according to JCN7 criteria were estimated using Cox model adjusted for potential confounding factors with normal BP treated as the reference category.

Results: We observed 689 CVD deaths. Hazard ratios for CVD mortality were progressively and significantly increased from the category of prehypertension. Population-attributable fraction (PAF) demonstrated that 43 and 48% of CVD and stroke deaths were explained by non-normal BP at baseline. Hazard ratios and PAF were remarkably higher in younger participants (aged 30–59 years) than those in the elderly (aged 60 years or above). Particularly, in younger men, 81% of CVD deaths were explained by non-normal BP. In sensitivity analysis, participants with antihypertensive medication showed the highest hazard ratio for CVD morality compared with the other categories.

Conclusions: BP levels above normal at baseline retained significant relative and absolute risks of CVD and stroke mortality during 24 years. Long-lasting burden of non-normal BP particularly in younger individuals suggests the importance of primary prevention of high BP from younger generation.

Keywords: blood pressure, cardiovascular disease, cerebral hemorrhage, cerebral infarction, long-term follow up, population-attributable fraction, stroke

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; ICD-10, 10th International Classification of Disease; ICD-9, 9th International Classification of Disease; PAF, population-attributable fraction

INTRODUCTION

High blood pressure (BP) has been shown to be an established risk factor for cardiovascular diseases (CVDs), although most findings were from studies with relatively shorter follow-up periods [1–7]. Several studies from Western populations revealed that BP measured at baseline predicted long-term (more than 20 years) future events of coronary heart disease (CHD) or stroke [8–11], even in young and middle-aged population. However, such evidence is scarce in Asian populations where stroke is dominant among CVDs [12].

We therefore investigated the association between BP measured at baseline and long-term mortality risk of total and subcomponents of CVD using 24-year follow-up of a representative Japanese population from a national survey, the National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged in 1980 (NIPPON DATA80), including young and middle-aged Japanese men and women aged 30 years or above. We also estimated population-attributable fraction (PAF) for corresponding CVD mortality.

METHODS

Participants and follow-up

The NIPPON DATA80 is a cohort of Japanese individuals participated in the National Survey on Circulatory Disorders in 1980. In 1980, 300 districts were randomly selected from all over Japan. All residents aged above 30 years who lived in the 300 districts – a total of 13730 people – were recruited by local public health centers and the baseline survey was carried out at these local health centers. A total of 10546 men and women from these 300 districts chose to participate in NIPPON DATA80 [5,13–16], a participation rate in the baseline survey of about 77%.

We excluded those who were lost to follow-up due to incomplete residential addresses at the baseline survey ($n = 913$). We further excluded participants with a history of CVD ($n = 257$), those treated with antihypertensive medication ($n = 746$), and those with missing information ($n = 38$) at the baseline survey. Consequently, 8592 participants (3781 men and 4811women) were eligible for the major analysis.

NIPPON DATA80 completed follow-up surveys until 2004. Vital status of the participants was followed by the basic resident register of local governments. To determine causes of death, we used the National Vital Statistics database of Japan with permission of the Ministry of Internal Affairs and Communications, Government of Japan. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Deaths from all CVDs (ICD-9: 393–459, ICD-10: I00–I99), CHD (ICD-9: 410–414, ICD-10: I20–I25), stroke (ICD-9: 430–438, ICD-10: I60–I69), cerebral infarction (ICD-9: 433 and 434, ICD-10: I63 and I69.3), and cerebral hemorrhage (ICD-9: 431 and 432, ICD-10: I61 and I69.1) were defined according to ICD-9 and ICD-10 codes. The Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000, No. 17–21–1, 2010) approved the study.

Biochemical and physical examinations

Public health nurses obtained data including smoking habit, as well as current health status and medical history. Smoking habit was categorized into nonsmoker, past smoker, and current smoker. Drinking habit was categorized into nondrinker, past drinker, and current drinker. BMI was calculated as weight (kg) divided by height (m)^2. BP was measured once by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest.

Nonfasting blood samples were collected and analyzed at one specific laboratory (Osaka Medical Center for Health Science and Promotion, Osaka, Japan) [17]. In 1980, blood glucose levels were measured at this site using the cupric-neocuproine method [18]. Because blood glucose levels are now widely measured using the hexokinase method, the levels were adjusted using a formula {[0.047 × (glucose concentration using the cupric-neocuproine method in mg/dl)] – 0.541}, as previously reported, which gives levels in mmol/l [17–19]. Serum total cholesterol was measured at the same laboratory using the Lieberman-Burchard direct method [20].

We defined hyperglycemia as a nonfasting serum glucose level of at least 7.77 mmol/l [19], or treatment for diabetes. We categorized the participants into four groups according to the Seventh Report of the Joint National Committee criteria based on SBP and DBP levels: normal BP (<120/80 mmHg), prehypertension (120–139/80–89 mmHg), stage 1 hypertension (140–159/90–99 mmHg), and stage 2 hypertension (≥160/100 mmHg) [21]. All participants treated with antihypertensive medication at baseline were excluded from the main analysis. In a sensitivity analysis, we additionally categorized all participants treated with antihypertensive medication at baseline as the 'antihypertensive medication group'. We also additionally categorized the participants into five groups according to the European Society of Hypertension/European Society of Cardiology (ESH/ESC) categorization, which is based on BP levels.

Statistical analysis

Multivariate-adjusted hazard ratios for total and subcomponents of CVD mortality in BP categories were estimated using Cox proportional hazards models adjusted for age, sex, smoking habit, drinking habit, BMI, serum total cholesterol, and the presence of hyperglycemia. We treated normal BP group as the reference. We also calculated the PAF components for total and subcomponents of CVD mortality in BP categories based on hazard ratios [22]. PAF was estimated as [pd × (hazard ratio − 1)/hazard ratios], where pd is the proportion of death cases arising from each category. We conducted a subgroup analysis by age group [younger group (30–59 years) versus elderly group (60 years or above]. To examine interaction by age group and BP categories on the effect of CVD mortality, an ordinal variable for BP categories was created and an interaction term with BP categories and age group were included in the models. Similarly, we also conducted a subgroup analysis by sex. All tests were two-tailed and a P value of less than 0.05 was considered statistically significant. All analyses were performed using SAS 9.13 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Total person-years were 182910 and mean follow-up period was 21.3 years. The baseline characteristics of the participants are shown in Table 1. Mean age was 49.4 years and mean SBP and DBP levels were 133.9 and 80.5 mmHg, respectively. At baseline, 18.9, 41.2, 26.0, and 13.9% of the participants had normal BP, prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively. Age, BMI, glucose, and total cholesterol levels increased as the BP categories increased ($P < 0.001$). The proportion of men was higher in higher BP categories ($P < 0.001$).

During the follow-up period, a total of 689 participants died of CVD; 135 deaths were due to CHD, and 321 were from all stroke (183 for cerebral infarction and 72 for cerebral hemorrhage). Crude mortality rate per 100000 person-years for total CVD and stroke was 376.7 and 175.5, respectively.

Table 2 shows adjusted hazard ratios [95% confidence interval (CI)] and PAFs according to BP categories.

TABLE 1. Baseline characteristics of study population

	Normal BP	Prehypertension	Stage 1 HT	Stage 2 HT	Total participants
Total number	1622	3538	2237	1195	8592
Age (year)	43.4 ± 10.9	46.7 ± 11.9	53.7 ± 12.2	57.7 ± 12.5	49.43 ± 12.8
Male (%)	29.8%	44.4%	48.7%	53.3%	44.0%
BMI (kg/m²)	21.7 ± 2.8	22.4 ± 3.0	23.1 ± 3.2	23.4 ± 3.4	22.6 ± 3.1
Total cholesterol (mg/dl)	181.0 ± 31.8	185.9 ± 32.3	192.1 ± 33.2	194.3 ± 35.8	187.8 ± 33.3
Blood glucose (mmol/l)	5.19 ± 1.43	5.39 ± 1.45	5.74 ± 1.92	5.94 ± 1.94	5.52 ± 1.67
SBP (mmHg)	109.6 ± 6.4	126.7 ± 6.6	144.1 ± 7.9	168.8 ± 16.0	133.9 ± 20.2
DBP (mmHg)	67.6 ± 6.6	77.4 ± 6.9	86.1 ± 7.6	96.8 ± 11.2	80.5 ± 11.9
Smoking					
Nonsmoker (%)	67.0%	57.7%	54.8%	51.2%	57.8%
Past smoker (%)	6.3%	8.2%	10.4%	12.4%	9.0%
Current smoker (%)	26.7%	34.1%	34.9%	36.4%	33.2%
Drinking					
Nondrinker (%)	59.3%	52.9%	51.3%	45.8%	52.7%
Past drinker (%)	2.7%	2.8%	2.9%	3.1%	2.8%
Current drinker (%)	38.0%	44.3%	45.9%	51.1%	44.5%
Hyperglycemia (%)	3.5%	5.3%	9.3%	12.6%	7.0%

NIPPON DATA80, 8592 men and women without medication of antihypertension aged 30 years and above in 1980. Values are number, rate (%), or mean ± SD. Normal BP, <120/80 mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 HT, 140–159/90–99 mmHg; stage 2 HT, ≥160/100 mmHg. Hyperglycemia was defined as casual plasma glucose≥7.77mmol/l or treatment for diabetes. HT, hypertension.

TABLE 2. Hazard ratios for deaths from total and subcomponents of cardiovascular diseases according to blood pressure categories

	Normal BP	Prehypertension	Stage 1 HT	Stage 2 HT	P for trends
Number of participants	1622	3538	2237	1195	
Total cardiovascular disease					
Number of death	38	177	246	228	
Crude morality rate[a]	103.8	227.6	532.0	1022.3	
HR (95% CI) (model 1)	1 (reference)	1.37 (0.96–1.95)	1.72 (1.22–2.43)	2.33 (1.64–3.30)	<0.001
HR (95% CI) (model 2)	1 (reference)	1.40 (0.98–1.99)	1.80 (1.27–2.55)	2.45 (1.72–3.50)	<0.001
Estimated excess deaths[b]		51	111	137	
PAF[b]		7.3%	16.0%	19.6%	
All stroke					
Number of death	16	75	117	113	
Crude morality rate[a]	43.7	96.5	253.0	506.6	
HR (95% CI) (model 1)	1 (reference)	1.38 (0.81–2.38)	1.97 (1.17–3.35)	2.81 (1.65–4.80)	<0.001
HR (95% CI) (model 2)	1 (reference)	1.40 (0.82–2.41)	2.02 (1.19–3.44)	2.89 (1.68–4.96)	<0.001
Estimated excess deaths[b]		21	60	75	
PAF[b]		6.6%	18.6%	23.1%	
Cerebral infarction					
Number of death	10	40	68	65	
Crude morality rate[a]	27.3	51.4	147.0	291.4	
HR (95% CI) (model 1)	1 (reference)	1.04 (0.52–2.09)	1.52 (0.78–2.96)	1.96 (0.99–3.86)	0.001
HR (95% CI) (model 2)	1 (reference)	1.03 (0.51–2.07)	1.49 (0.76–2.93)	1.92 (0.96–3.82)	0.002
Estimated excess deaths[b]		1	23	32	
PAF[b]		0.6%	12.4%	17.1%	
Cerebral hemorrhage					
Number of death	3	14	27	28	
Crude morality rate[a]	8.2	18.0	58.4	125.5	
HR (95% CI) (model 1)	1 (reference)	1.55 (0.44–5.39)	3.06 (0.92–10.22)	5.11 (1.52–17.20)	<0.001
HR (95% CI) (model 2)	1 (reference)	1.68 (0.48–5.88)	3.52 (1.04–11.86)	5.99 (1.75–20.58)	<0.001
Estimated excess deaths[b]		6	19	23	
PAF[b]		7.9%	26.8%	32.4%	
Coronary heart disease					
Number of death	8	42	44	41	
Crude morality rate[a]	21.9	54.0	95.1	183.8	
HR (95% CI) (model 1)	1 (reference)	1.59 (0.74–3.39)	1.54 (0.72–3.29)	2.16 (1.00–4.69)	0.05
HR (95% CI) (model 2)	1 (reference)	1.58 (0.74–3.37)	1.49 (0.69–3.21)	2.03 (0.92–4.46)	0.10
Estimated excess deaths[b]		16	15	21	
PAF[b]		11.5%	10.8%	15.2%	

NIPPON DATA80, 8592 men and women without mediation of antihypertension aged 30 years and above in 1980. Model 1was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, serum total cholesterol, hyperglycemia, smoking habit, and drinking habit. 95% CI, 95% confidence interval; BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction.
[a]Crude rates per 100 000 person-years for each death stratified by BP categories.
[b]Estimated excess death and PAF were calculated using HRs in model 2. Normal BP, <120/80mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 HT, 140–159/90–99 mmHg; stage 2 HT, ≥160/100 mmHg. Hyperglycemia was defined as casual plasma glucose ≥7.77mmol/l or treatment for diabetes.

– 73 –

Compared with normal BP, the adjusted hazard ratios for total CVD mortality with prehypertension, stage 1 hypertension, and stage 2 hypertension were significantly raised. We additionally categorized the participants with prehypertension into two groups: normal BP (120–129/80–84 mmHg) and high-normal BP (130–139/85–89 mmHg), according to the ESH/ESC categorization (supplemental table 1, http://links.lww.com/HJH/A202). Compared with optimal BP in the ESH/ESC categorization, the hazard ratios for total CVD mortality increased progressively from normal BP to high-normal BP, as per the ESH/ESC categorization. However, the differences were not statistically significant. The risks of total and subtypes of stroke mortality also progressively increased relative to the normal BP group (*P* for trend = 0.002 for cerebral infarction, *P* for trend < 0.001 for total stroke and cerebral hemorrhage). In terms of the magnitude of the hazard ratio, the risk for cerebral hemorrhage in stage 2 hypertension was remarkably high (hazard ratio 5.99, compared with the normal BP group). Although not significant, a similar tendency was observed for CHD mortality. Higher BP above normal explained 42.9% of total CVD deaths, 37.5% of CHD deaths,

48.3% of death from total stroke, 30.1% from cerebral infarction, and 67.1% from cerebral hemorrhage.

Table 3 shows the adjusted hazard ratios (95% CI) and PAFs according to BP categories by age groups. Adjusted hazard ratios for total CVD, CHD, and stroke mortality for prehypertension, stage 1 hypertension, and stage 2 hypertension increased with increasing BP category, in both groups, younger and old, although these associations were more pronounced in the younger group as compared with the elderly group (*P* for interaction for total CVD = 0.007). Consistently with the magnitude of hazard ratios, PAFs associated with higher BP above normal were remarkably higher in the younger group than those in the elderly group (60.7 and 27.4% for total CVD deaths, respectively). For all stroke deaths, they were 65.8% in the younger group and 31.2% in the elderly group.

Table 4 shows the adjusted hazard ratios (95% CI) and PAFs for total CVD mortality according to BP categories by age groups stratified by sex. Adjusted hazard ratios progressively increased from the normal BP group in all categories (all *P* for trend < 0.02). In both men and women, these associations tended to be more remarkable in the

TABLE 3. Multivariate-adjusted hazard ratios for deaths from total and subcomponents of cardiovascular diseases according to blood pressure categories stratified by age

	Normal BP	Prehypertension	Stage 1 HT	Stage 2 HT	P for trends
Aged 30–59 years					
Number of participants	1478	3029	1565	692	
Total cardiovascular disease					
Number of death	12	60	67	64	
HR (95% CI)	1 (reference)	1.93 (1.03–3.59)	2.74 (1.46–5.13)	5.25 (2.78–9.90)	<0.001
Estimated excess deaths		29	43	52	
PAF		14.2%	21.0%	25.5%	
All stroke					
Number of death	5	26	30	36	
HR (95% CI)	1 (reference)	1.99 (0.76–5.19)	2.97 (1.13–7.80)	7.31 (2.79–19.14)	<0.001
Estimated excess deaths		13	20	31	
PAF		13.3%	20.5%	32.0%	
Coronary heart disease					
Number of death	3	15	13	14	
HR (95% CI)	1 (reference)	1.88 (0.54–6.52)	1.89 (0.53–6.80)	3.80 (1.05–13.69)	0.03
Estimated excess deaths		7	6	10	
PAF		15.6%	13.6%	22.9%	
Aged 60 years and above					
Number of participants	144	509	672	503	
Total cardiovascular disease					
Number of death	26	117	179	164	
HR (95% CI)	1 (reference)	1.15 (0.75–1.76)	1.41 (0.93–2.14)	1.68 (1.10–2.56)	0.001
Estimated excess deaths		15	52	66	
PAF		3.1%	10.7%	13.6%	
All stroke					
Number of death	11	49	87	77	
HR (95% CI)	1 (reference)	1.11 (0.58–2.14)	1.56 (0.82–2.93)	1.78 (0.93–3.40)	0.006
Estimated excess deaths		5	31	34	
PAF		2.2%	13.9%	15.1%	
Coronary heart disease					
Number of death	5	27	31	27	
HR (95% CI)	1 (reference)	1.40 (0.53–3.66)	1.26 (0.48–3.27)	1.46 (0.55–3.91)	0.63
Estimated excess deaths		8	6	9	
PAF		8.5%	7.0%	9.5%	

NIPPON DATA80, 8592 men and women without medication of antihypertension aged 30 years and above in 1980. Hazard ratios were adjusted for age, sex, BMI, serum total cholesterol, hyperglycemia, smoking habit and drinking habit. Normal BP, <120/80 mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 HT, 140–159/90–99 mmHg; stage 2 HT, ≥160/100 mmHg. Hyperglycemia was defined as casual plasma glucose ≥7.77 mmol/l or treatment for diabetes. 95% CI, 95% confidence interval; BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction. *P* values for interaction by age group were 0.007, 0.32, and 0.03 for death from the total cardiovascular disease, coronary heart disease, and all stroke, respectively.

— 74 —

TABLE 4. Multivariate-adjusted hazard ratios for deaths from cardiovascular diseases according to blood pressure categories stratified by sex and age

	Normal BP	Prehypertension	Stage 1 HT	Stage 2 HT	P for trends
Men					
Aged 30–59 years					
Number of participants	440	1351	806	395	
Number of death	3	34	44	44	
HR (95% CI)	1 (reference)	3.84 (1.18–12.52)	5.72 (1.76–18.53)	10.74 (3.29–34.98)	<0.001
Estimated excess deaths		29	43	52	
PAF		20.1%	29.0%	31.9%	
Aged 60 years and above					
Number of participants	44	219	284	242	
Number of death	9	54	82	82	
HR (95% CI)	1 (reference)	1.10 (0.54–2.25)	1.37 (0.69–2.76)	1.78 (0.88–3.61)	0.005
Estimated excess deaths		5	22	36	
PAF		2.2%	9.8%	15.9%	
Women					
Aged 30–59 years					
Number of participants	1038	1678	759	297	
Number of death	9	26	23	20	
HR (95% CI)	1 (reference)	1.36 (0.63–2.93)	1.68 (0.75–3.77)	3.39 (1.47–7.85)	0.002
Estimated excess deaths		7	9	14	
PAF		8.8%	11.9%	18.1%	
Aged 60 years and above					
Number of participants	100	290	388	261	
Number of death	17	63	97	82	
HR (95% CI)	1 (reference)	1.18 (0.69–2.02)	1.47 (0.87–2.49)	1.65 (0.97–2.83)	0.017
Estimated excess deaths		9	31	32	
PAF		3.7%	12.0%	12.5%	

NIPPON DATA80, 8592 men and women without medication of antihypertension aged 30 years and above in 1980. Hazard ratios were adjusted for age, sex, BMI, serum total cholesterol, hyperglycemia, smoking habit, and drinking habit. Normal BP, <120/80 mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 HT, 140–159/90–99 mmHg; stage 2 HT, ≥160/100 mmHg. Hyperglycemia was defined as casual plasma glucose ≥7.77 mmol/l or treatment for diabetes. 95% CI, 95% confidence interval; BP, blood pressure; HT, hypertension; HR, hazard ratio; PAF, population-attributable fraction. Higher BP above normal explained 81% of CVD deaths in younger men, 28% of CVD deaths in elderly men, 39% of CVD deaths in younger women and 28% of CVD deaths in elderly women. P values for interaction by sex were 0.31 and 0.99 for the younger group and elder group, respectively. P values for interaction by age group were 0.07 and 0.33 for the men and women, respectively.

younger group as compared with the elderly group, although there was no evidence of statistically significant heterogeneity (all P values for interaction >0.07). PAFs for CVD deaths associated with higher BP above normal were the highest in younger men: 81% of CVD deaths occurred during 24 years was explained by higher BP above normal at baseline examination.

Table 5 shows the adjusted hazard ratios (95% CI) according to BP categories, including the participants on antihypertensive medication. Adjusted hazard ratios for total CVD, all stroke, and CHD death in the antihypertensive medication group were higher than the hazard ratios for stage 2 hypertension. However, the adjusted hazard ratio for death from cerebral hemorrhage for stage 2

TABLE 5. Multivariate-adjusted hazard ratios for deaths from total and subcomponents of cardiovascular diseases

	Normal BP	Prehypertension	Stage 1 HT	Stage 2 HT	Hypertension medication
Number of participants	1622	3538	2237	1195	745
Total cardiovascular disease					
Number of death	38	177	246	228	211
HR (95% CI)	1.00	1.40 (0.99–1.99)	1.80 (1.28–2.55)	2.48 (1.74–3.53)	2.96 (2.07–4.24)
All stroke					
Number of death	16	75	117	113	99
HR (95% CI)	1.00	1.41 (0.82–2.43)	2.05 (1.21–3.48)	2.94 (1.72–5.03)	3.41 (1.97–5.90)
Cerebral infarction					
Number of death	10	19	21	68	65
HR (95% CI)	1.00	1.06 (0.53–2.12)	1.55 (0.79–3.04)	2.03 (1.02–4.02)	2.71 (1.36–5.41)
Cerebral hemorrhage					
Number of death	3	14	27	28	16
HR (95% CI)	1.00	1.64 (0.47–5.73)	3.37 (1.00–11.33)	5.67 (1.66–19.30)	4.82 (1.34–17.36)
Coronary heart disease					
Number of death	8	42	44	41	41
HR (95% CI)	1.00	1.58 (0.74–3.37)	1.50 (0.70–3.23)	2.09 (0.96–4.57)	2.64 (1.19–5.82)

NIPPON DATA80, 9337 men and women with and without medication of antihypertension aged 30 years and above in 1980. Hazard ratios were adjusted for age, sex, BMI, serum total cholesterol, hyperglycemia, smoking habit, and drinking habit. Normal BP, <120/80 mmHg; prehypertension, 120–139/80–89 mmHg; stage 1 HT, 140–159/90–99 mmHg; stage 2 HT, ≥160/100 mmHg; hypertension medication, medication of antihypertension. Hyperglycemia was defined as casual plasma glucose ≥7.77 mmol/l or treatment for diabetes. 95% CI, 95% confidence interval; BP, blood pressure; HT, hypertension; HR, hazard ratio.

hypertension was higher than the hazard ratio in the antihypertensive medication group.

DISCUSSION

On the basis of this 24-year observation of the representative Japanese population, we demonstrated that BP predicted long-term risk of mortality for total and subcomponents of CVD. Compared with normal BP, adjusted hazard ratios in stage 1 hypertension and stage 2 hypertension for total CVD death were significantly high, whereas higher BP above normal at baseline explained more than 40% of CVD deaths and approximately 50% of stroke deaths. Corresponding hazard ratios and PAFs were remarkably higher in younger (aged 30–59 years) than those in the elderly (aged at 60 years or above) participants. Particularly, in younger men, nonnormal BP at baseline explained 81% of CVD deaths during the subsequent 24 years.

Several studies in the Western populations demonstrated consistent association between BP and subsequent CVD risk based on long-term observation. The Framingham study reported that increase in BP categories was associated with higher lifetime risk of stroke events during 30 years in both men and women at 55 years of age [11]. A 28-year follow-up study from Göteborg, Sweden, reported a sig-·nificant association between SBP categories and stroke events in men aged 47–55 years [10]. A 25-year follow-up study from Chicago Heart Study showed a significant association between BP categories and mortality due to coronary heart disease and cardiovascular diseases in US men aged 18–39 years [8].

Regarding non-Western populations, the Hisayama study, conducted in a Japanese town, reported a long-term association between BP and stroke risk in men and women aged 40 years or above [23,24]. However, in their analysis, hazard ratios according to the BP categories were estimated by a time-dependent Cox's proportional hazards model, in which risk factors other than age and sex were allowed to change in accordance with data derived from examinations conducted approximately every 5 years during the follow-up period (32 years) [23,24]. Therefore, to our knowledge, this is the first study that directly examines the long-term association between baseline BP and total and subcomponents of CVD in a non-Western population. Moreover, the large number of participants derived from a nationwide stratified random sample was a strength of the present study. We previously reported the association between BP categories and risk of CVD death in the NIPPON DATA80 [5,13]. However, the association between BP and subcomponents of CVD was not examined in these analyses because of smaller number of CVD deaths attributable to relatively shorter follow-up period.

Our results demonstrated that higher BP levels at baseline were a long-lasting clinical and public health problem. Particularly in younger participants, long-term excess risk associated with high BP was large (61% for CVD deaths). Similar findings for men were observed in cohorts of young Western men [8,10]. These results indicate the importance of population-wide primary prevention through lifestyle modification such as salt reduction [25] as well as the necessity for early detection of high BP in young men,

both in Western and non-Western populations. However, generalizability of these findings to young women could not be tested in previous Western studies that did not include women. In contrast, in the present study, we revealed that the long-term excess risk associated with high BP in younger men was remarkably higher than that in younger women (81% for total CVD death in men and 39% in women). To our knowledge, this is the first study to demonstrate a sex difference in long-term excess risk associated with high BP in younger individuals.

In the present study, the risk associated with higher BP was more marked for cerebral hemorrhage than cerebral infarction. PAF for cerebral hemorrhage due to hypertension was approximately 60%, which was 1.4-fold larger compared with PAF for all stroke. In Japan, the trends in BP reported by the Japanese National Nutrition and Health Survey showed that the BP declined substantially during the years 1965–1990 for men and women in all age groups [26]. Concomitantly, mortality from stroke, especially cerebral hemorrhage, declined greatly [12,26]. Our results could be considered to be consistent with these long-term changes observed in Japan.

In the present study, the adjusted hazard ratio for CVD death in the antihypertensive medication group was higher than that for stage 2 hypertension. These observations might be due to inadequate BP control in the antihypertensive medication group. In the antihypertensive medication group, the mean BP was $158 \pm 21/90 \pm 13$ mmHg. Moreover, the difference in duration of hypertension in the antihypertensive medication group and the stage 2 hypertension group might explain our result.

We additionally examined the association between BP categories and future non-CVD death. We found that the risk of non-CVD death in stage 2 hypertension was slightly but significantly increased (supplemental Table 1, http://links.lww.com/HJH/A202). Possible reasons for the results might be that some of the participants died from noncardiovascular causes due to after-effect of CVD incidence (such as aspiration pneumonia), and that several lifestyle-related risk factors for hypertension (such as salt and alcohol consumption) increased the risk of noncardiovascular death.

The study has several limitations. First, the numbers of events were not enough to permit stratified analysis by more detailed age decades. Second, we could not control the influence of start of antihypertensive medication after baseline survey, since we did not have any information on it. Third, we did not adjust for socioeconomic status because the data were not available. However, since all Japanese citizens have been covered by the universal health insurance system about 20 years prior to the baseline survey of the present study, socioeconomic status would not largely affect access to treatment [27]. Therefore, we believe that the effect of difference in socioeconomic status on our finding might be minimal. We used the National Vital Statistics of Japan as an endpoint, which might lead to misclassification of death. However, in Japan, the number of computed tomography (CT) and MRI scanners per million population is the highest among Organization for Economic Co-operation and Development countries. Therefore, the diagnosis of cerebral infarction and cerebral

hemorrhage during the follow-up period was considered to be reliable. BPs were measured once, which might lead to misclassification of BP categories. However, such misclassification might tend to underestimate the impact of BP on CVD. In the present study, we did not examine the association between BP and long-term future CVD death using a time-dependent Cox proportional hazard model, because in the study, BPs were not measured at the follow-up survey. In the present study, 8.7% of participants were lost to follow-up, because we could not identify their local government residency registration, due to incomplete residential addresses at the baseline survey. The participants who were lost to follow-up were younger, higher prevalence of men, and having lower BP. However, after adjustment for age and sex, there was no statistically significant difference between BP in the participants who were followed up and BP in those who were lost to follow-up (data not shown).

In conclusion, in a nationwide, representative sample of the Japanese population, higher BP predicted both total CVD mortality and subcomponent risk, over a period of more than 20 years. More than 40% of CVD deaths and approximately 50% of stroke deaths that occurred during the 24 years were explained by a baseline BP that was above normal. The excess risk was particularly large in younger men. Population-wide lifestyle modification to prevent higher levels of BP and management of hypertension at an early stage should be emphasized.

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Conflicts of interest
Disclosures: All authors disclose no financial conflicts of interest. The sponsors did not participate in the design or conduct of the study; the collection; management, analysis, and interpretation of the study; or the preparation, review, or approval of the manuscript.

REFERENCES

1. Cressman MD, Gifford RW Jr. Hypertension and stroke. *J Am Coll Cardiol* 1983; 1:521–527.
2. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al.* Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.
3. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993; 153:598–615.
4. Whelton PK. Epidemiology of hypertension. *Lancet* 1994; 344:101–106.
5. NIPPON DATA80 Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese: Nippon data 80. *J Hum Hypertens* 2003; 17:851–857.
6. Lawes CM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, *et al.* Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens* 2003; 21:707–716.
7. Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, *et al.* Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertens Res* 2005; 28:901–909.
8. Miura K, Daviglus ML, Dyer AR, Liu K, Garside DB, Stamler J, *et al.* Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med* 2001; 161:1501–1508.
9. Qureshi AI, Suri MF, Mohammad Y, Guterman LR, Hopkins LN. Isolated and borderline isolated systolic hypertension relative to long-term risk and type of stroke: a 20-year follow-up of the national health and nutrition survey. *Stroke* 2002; 33:2781–2788.
10. Harmsen P, Lappas G, Rosengren A, Wilhelmsen L. Long-term risk factors for stroke: twenty-eight years of follow-up of 7457 middle-aged men in Goteborg, Sweden. *Stroke* 2006; 37:1663–1667.
11. Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, *et al.* The lifetime risk of stroke: estimates from the Framingham Study. *Stroke* 2006; 37:345–350.
12. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, *et al.* Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008; 118:2702–2709.
13. Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *J Hypertens* 2006; 24:459–462.
14. Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, *et al.* Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004; 35:1836–1841.
15. Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Elliott P, *et al.* Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. *Am Heart J* 2004; 147:1024–1032.
16. NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J* 2006; 70:1249–1255.
17. Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, *et al.* The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. *Atherosclerosis* 2007; 190:216–223.
18. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, *et al.* Type 2 diabetes and risk of nonembolic ischaemic stroke in Japanese men and women. *Diabetologia* 2004; 47:2137–2144.
19. Kadowaki S, Okamura T, Hozawa A, Kadowaki T, Kadota A, Murakami Y, *et al.* Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population. NIPPON DATA80. *Diabetologia* 2008; 51:575–582.
20. Nakamura Y, Yamamoto T, Okamura T, Kadowaki T, Hayakawa T, Kita Y, *et al.* Combined cardiovascular risk factors and outcome: NIPPON DATA80, 1980–1994. *Circ J* 2006; 70:960–964.
21. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al.* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
22. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; 88: 15–19.
23. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, *et al.* Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke* 2000; 31:2616–2622.

24. Arima H, Tanizaki Y, Yonemoto K, Doi Y, Ninomiya T, Hata J, *et al.* Impact of blood pressure levels on different types of stroke: the Hisayama study. *J Hypertens* 2009; 27:2437–2443.

25. Appel LJ, Frohlich ED, Hall JE, Pearson TA, Sacco RL, Seals DR, *et al.* The importance of population-wide sodium reduction as a means to prevent cardiovascular disease and stroke: a call to action from the American Heart Association. *Circulation* 2011; 123:1138–1143.

26. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J Atheroscler Thromb* 2007; 14:278–286.

27. Fukawa T. *Public health insurance in Japan. The International Bank for Reconstruction and Development/the World Bank.* Washington, DC: The World Bank; 2002.

Reviewers' Summary Evaluations

Reviewer 1

The authors assess the long-term prognostic significance of BP in an Asian population, in which such data are scarce. With normal BP as the reference the fully adjusted hazard ratio for cardiovascular mortality and death from stroke and coronary heart disease increased progressively from pre-hypertension to stage 1 and 2 hypertension, but was not significant in prehypertension. In a secondary analysis, the hazard ratio was not significantly different between optimal BP and normal and high normal BP. By contrast, other studies observed significant differences within the non-hypertensive range. Limitations of the current study are that BP was only measured once and that the analysis was restricted to mortality, which limits the clinical relevance and the power of the study.

Reviewer 2

Strengths: The study investigated the association between baseline BP and cardiovascular mortality over a 24 years' observation period in a Japanese population where stroke is the main cause of cardiovascular death. Such an association is well established in Western populations but has not been documented yet in an Asian population. The study showed that 81% of cardiovascular deaths were explained by BP values $\geq$120/80 mmHg.

Weaknesses: A total of 913 individuals were excluded from the analysis because they were lost to follow-up. This is a non-negligible proportion of the study population (8.6%) which is a major study limitation.

Another weakness of the study was only one BP measurement with a standard mercury sphygmo-manometer.

— 78 —

(4)日本における飽和脂肪酸摂取と冠疾患死亡との関連 NIPPON DATA90, 1990-2005

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目的：

　飽和脂肪酸摂取と冠疾患リスクとの関連については欧米の前向き研究結果に一致をみないし、またわが国での当該研究は数少ない。本研究の目的は食餌性の総脂肪、飽和脂肪酸、多価不飽和脂肪酸、およびコレステロール摂取と冠疾患死亡との関連をNIPPON DATA90データセットを用いて検討することである。

方法：

　1990年に無作為抽出した全国300ヵ所において30才以上の男女を対象として検診と生活習慣調査を行い、心筋梗塞または脳卒中の既往のない7,819人(男性3,254人、女性4,565人)を15年間追跡した。国民栄養調査で得られた世帯分の栄養素量を、世帯員の性・年齢を考慮して個人分に按分計算することにより按分推定量を求めた。さらに総摂取熱量当たりの按分推定量を計算して摂取濃度（単位は%kcal, mg/1000kcalなど）を求めた。

結果：

　追跡期間中に冠疾患死亡が男性で40人、女性で30人あった。飽和脂肪酸、多価不飽和脂肪酸の平均摂取量は男性でそれぞれ5.90±1.36%、5.59±1.30%であり、女性で6.48±1.53%、6.08±1.14%であった。年齢、野菜、果物摂取量および他の交絡因子で調整したCox解析により女性において飽和脂肪酸摂取量は冠疾患死亡と有意な正の関

連があった(5 分位摂取量の 1 分位上昇によるハザード比=1.34, 95%信頼区間:
1.02-1.74, P=0.03)。一方男性ではこのような関連は認められなかった。男女とも他の
脂肪酸およびコレステロールと冠疾患死亡には関連が見られなかった。

結論：
　女性において飽和脂肪酸摂取量は他の交絡因子とは独立して冠疾患死亡と有意な正
の関連があったが、男性ではこの関連は認められなかった。

Current Nutrition and Food Science in press

Fatty Acid Intakes and Coronary Heart Disease Mortality in Japan: NIPPON DATA90, 1990-2005

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Abstract: Associations between dietary fatty acid intakes and risk of coronary heart disease (CHD) are not entirely consistent in prospective studies in the U.S. and Europe. Such studies in Japan are rare. The objective of this study was to examine the association between dietary total, saturated (SFA), and polyunsaturated (PUFA) fatty acids, cholesterol intake and CHD mortality using the dataset of NIPPON DATA90. At the baseline in 1990, we performed blood biochemical measurements and a nutritional survey on participants from 300 randomly selected districts. After exclusion of participants with a history of CHD and/or stroke at the baseline, we followed 7,819 community residents (3,254 men and 4,565 women, age ≥ 30) for 15 years. We estimated individual nutrient intakes among family members by weighed food records in three consecutive representative days. During the follow-up, there were 42 CHD deaths in men and 30 in women. Mean daily SFA and PUFA % calorie intakes were 5.90±1.36%, and 5.59±1.30%, respectively in men, and 6.48±1.53%, and 6.08±1.14% in women. A Cox analysis adjusted for age, vegetable and fruit intakes, and other confounders in women found that SFA intake was significantly associated with CHD mortality (hazards ratio per one quintile increment=1.34, 95% confidence intervals: 1.02-1.74, P=0.03), while no such association was noted in men. No associations were found between other fat intakes and CHD mortality in men or women. In conclusion, SFA intake was positively associated with CHD mortality independent of confounders in women, but not in men.

Key Words: Cohort study, coronary heart disease, fatty acid intakes, mortality, saturated fatty acids, polyunsaturated fatty acids.

INTRODUCTION

Associations between dietary intakes of saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and risk of coronary heart disease (CHD) are not entirely consistent in prospective studies in the U.S. and Europe. In some studies, SFA intake was found to be positively associated with CHD incidence [1, 2] and CHD mortality [3-7], whereas other studies found no association between SFA intake and CHD mortality [8-12]. PUFA intake was found to be inversely associated with CHD incidence [10, 13] and CHD mortality [6, 11] in some studies, but other studies found no association [1, 3, 7, 8, 10, 14-17]. Such studies in Japan, where intake of SFA is relatively low and intake of PUFA is relatively high, are rare [18]. We examined the association between total dietary fat, SFA, PUFA, as well as dietary cho-

lesterol intake and CHD mortality, using the dataset of NIPPON DATA90.

PARTICIPANTS AND METHODS

Participants

Cohort studies of the National Survey on Circulatory Disorders, Japan, are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged). NIPPON DATA included two cohort studies. We performed the baseline surveys in 1980 and 1990 (NIPPON DATA80 and NIPPON DATA90). We reported the details of these cohorts previously [19-22]. In the present study, we analyzed more recent data from NIPPON DATA90.

A total of 8,384 community residents (3,504 men and 4,880 women, aged 30 and older) from 300 randomly selected districts participated in the survey and were followed

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until November 15th, 2005. The overall population aged 30 and over in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population. Of the 8,384 participants, we excluded 565 for the following reasons: self-reported past history of coronary heart disease or stroke obtained by a questionnaire (n=262), information missing at the baseline survey (n=19), and failure to access due to incomplete residential access information at the first survey (n=284). We included the remaining 7,819 participants (3,254 men and 4,565 women) in the analysis.

Follow-up Survey

To determine the cause of death over 15 years of follow-up, we used the National Vital statistics database of Japan with permission from the Management and Coordination Agency, Government of Japan. We coded the underlying causes of death according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and ICD-10 from the beginning of 1995. We described the details of the classification in the present study elsewhere [23]. We identified cardiovascular diseases (CVD) (ICD-9: 393 to 459 and ICD-10: I00 to I99), CHD (ICD-9: 410 to 414 and ICD-10: I20 to I25), heart failure (HF) (ICD-9: 428 and ICD-10: I50), and stroke (ICD-9: 430 to 438 and ICD-10: I60 to I69). We obtained approval for the study from the Institutional review Board of Shiga University of Medical Science (No. 12-18, 2000).

Baseline Examination

At the baseline in 1990, we obtained non-fasting blood samples. We separated the serum and centrifuged it soon after blood coagulation. We also obtained plasma samples in a siliconized tube containing sodium fluoride. We shipped these samples to one laboratory (SRL, Tokyo) for blood measurements. We measured plasma glucose and serum total cholesterol (TCH) enzymatically. We measured high-density lipoprotein cholesterol (HDL) by the precipitation method using heparin-calcium. We calculated non-HDL (nonHDL) cholesterol as TCH − HDL. Lipid measurements were standardized by the Centers for Disease Control / National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipids Standardization Program [24].

We calculated body mass index (BMI) as weight (kg) divided by height squared (m). Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants. Public health nurses obtained information about smoking, drinking, and medical histories. We divided participants into three categories of smoking (never-smoked; ex-smoker; current smoker, 1 to 9, 10 to 19, and ≥20 cigarettes/day) and three categories of drinking (never-drinker; ex-drinker; current drinker). We defined hypertension as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, the use of antihypertensive agents, or any combination of these. We defined diabetes as a fasting blood sugar level ≥140mg/dl, or if less than 8 hours after meals≥200mg/dl, or participants diagnosed as having diabetes.

Nutritional Survey

We used the data of the National Nutritional Survey in Japan (NNSJ). In the NNSJ, a food intake survey by weighed food records over three consecutive representative days was conducted by specially trained dietary interviewers. Dietary interviewers visited participants' houses at least once during the survey. We avoided weekends and holidays. We used the Updated Standard Tables for Food Composition in Japan, 4th edition, with matched fatty acid values and micronutrients, to calculate Japanese nutrient intakes. Before 1995, the dietary records did not include information on the portion of each food that each household member actually ate. We estimated the nutrient intake of each household member by dividing household intake data of the NNSJ90 conducted in 1990 proportionally using average intakes by sex and age groups calculated for the NNSJ conducted in 1995, when collection of information on food consumption of individual household members started. Detailed methods are described elsewhere [23]. For each person, means of the estimated individual nutrients from the three days' records were used in the analyses. We presented data as the contribution to total energy intake (%kcal) from total fat, SFA, PUFA; dietary cholesterol (mg/1000 kcal); vegetables, fruits, fish, meats and eggs (g/1000kcal).

Data Analyses

We analyzed data in men and women separately. We examined CHD cases, age, fatty acid intake, intake of food groups, serum lipid profiles, BMI, prevalence of hypertension, diabetes, and current smokers and drinkers by quintile of SFA intake. We showed age data as the mean±SD. As for continuous variables except for age, we obtained age-adjusted data by analysis of covariance, and we showed these data as the mean±SE. Prevalence is shown as a %. To obtain the trend P for age, and the age-adjusted trend P for other variables, we used the "contrast" option for analysis of variance or covariance for continuous variables, and logistic analysis for prevalence variables. We calculated the multivariate adjusted hazards ratio (HR) for CHD mortality using a Cox's proportional hazards model. Model 1 included age to obtain the HR for a *one increment in quintile in SFA intake*. In addition to age, model 2 included hypertension, diabetes, BMI (<18.5, 18.5-25, 25-30 and >30 kg/m²; 18.5-25 served as a reference), smoking (never-smoked; ex-smoker; current smoker; never-smoked served as a reference), and drinking (never-drinker; ex-drinker; current drinker; never-drinker served as a reference). Finally, in model 3, we added intakes of vegetables, fruits, and fish (g/1000kcal) to model 2. To examine the effects of a one quintile increment in intakes of total fat, PUFA or dietary cholesterol, we used models 1 to 3 by replacing SFA with total fat, PUFA or dietary cholesterol. We also performed a Cox analysis on the effect of SFA intake on CHD mortality dichotomizing SFA intake at 7% of total energy intake (Model 4). In addition, we tested whether there was a regional difference in the association of SFA intake and CHD mortality, and an area block variable (1 to 9, from north to south) was added to model 4 (area 1 served as a reference). We tested proportionality by generating time-dependent covariates by creating interactions of the predictors and a function of survival time and included them in the models. None of these were significant. Also, by using a

"test" statement, we tested all the time-dependent covariates at once. This also not significant either. We confirmed the linearity assumption by plotting each continuous predictor variable against the Martingale residuals from a Cox model.

RESULTS

Descriptive Statistics

At the baseline in men, mean total energy intake, mean percentages (±SD) of energy from total dietary fat, SFA, and PUFA were 2322±462 kcal, 22.3±4.5%, 5.9±1.4%, and 5.6±1.3%, respectively; mean intake of dietary cholesterol was 183.6±53.2 mg/1000kcal. Those values in women were 1865±366 kcal, 24.4±5.0%, 6.5±1.5%, 6.1±1.4%, and 200.6±59.0 mg/1000kcal, respectively. We followed participants for an average of 13.9±2.9 y. During follow-up (108,684 person-years), we noted 72 CHD deaths (42 [acute myocardial infarction=25, other CHD=17] in men, and 30 [acute myocardial infarction=21, other CHD=9] in women).

Baseline characteristics by quintile of SFA intake in men are shown in Table 1 and in Table 2 for women. In men, mean PUFA, fruit, meat, egg intakes, TCH and nonHDL concentrations were significantly greater in the higher SFA intake groups (age-adjusted trend Ps <0.001). Mean age, intake of vegetables, and fish; the prevalence of hypertension and current drinkers was significantly lower in the higher SFA intake groups (age-adjusted trend Ps 0.003 to <0.001). Mean total energy intake and BMI, the prevalence of diabetes and smokers were not different across the groups. In women, mean PUFA, fruit, meat, egg intake; TCH, HDL, and nonHDL concentration; and prevalence of current smokers were significantly greater in the higher SFA intake groups (age-adjusted trend Ps 0.003 to<0.001). Mean age, intakes of vegetables, and fish, BMI, and prevalence of hypertension were significantly lower in the higher SFA intake groups (age-adjusted trend Ps <0.001). Mean total energy intake, prevalence of diabetes, and current drinkers were not different across the groups.

Associations of SFA, PUFA, Total Fat, and Cholesterol Intakes with CHD Mortality

The results of the analyses on the associations of SFA, PUFA, total fat, and cholesterol intakes with CHD mortality using a Cox's proportional hazards model in men and women are shown in Table 3. In men, no associations were observed between CHD mortality and the quintiles of SFA, PUFA, total fat, or cholesterol intake. In women, SFA intake was significantly positively associated with CHD mortality in all models (HR for 1 increment in quintile of SFA intake: model 1 HR=1.38, 95% confidence intervals [CI] 1.06-1.78, P= 0.016; model 2 HR=1.41, 95% CI 1.09-1.84, P=0.010; model 3 HR=1.34, 95% CI 1.02-1.74, P=0.034). Intake of SFA higher than 7% of total energy intake in women was also significantly positively associated with CHD mortality in model 4 (HR=2.59, 95% CI 1.19-5.63, P=0.016), but not in men. Analysis with the addition of an area block variable to model 4 detected no regional differences in the association of SFA intake and CHD mortality. Although total fat intake was marginally associated with CHD mortality, none of the

other dietary fat intakes except for SFA were significantly associated with CHD mortality.

DISCUSSION

Previous metabolic ward studies have demonstrated that SFA intake increases are the primary determinant of serum cholesterol, while changes in low-density lipoprotein cholesterol (LDL) roughly parallel the changes in serum cholesterol [25-27]. Thus, a higher SFA intake is expected to be associated with a higher incidence and mortality from CHD. In this large cohort of middle-age men and women with relatively low intake of total dietary fatty acids and SFA, we found that SFA intake was significantly positively associated with CHD mortality in women, but not in men. Total fat, PUFA and dietary cholesterol intakes were not associated with CHD mortality in men or women. Our findings were consistent in three different models with increasing numbers of possible confounding factors.

In previous studies conducted in the US and European countries, the mean dietary total fat and SFA were reported to be around 35% and 12% [1, 7, 13, 14]; these values in our participants were substantially lower at 24.4%, and 6.5%, respectively. It has been reported that the current American diet contains an average of about 11% of total calories as SFA [28]. The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) recommends that SFA should be consumed at less than 7% of total calories in order to maintain a healthy level of LDL [28]. Although the mean SFA intake was less than this level, about 20% of our male participants and 30% of our female participants exceeded this recommendation. Actually in the present study, SFA intake >7% of total calories in women was significantly positively associated with CHD mortality, but not in men. This difference between men and women in the effect of SFA on CHD outcome was similarly observed in previous studies from the US and Europe [4, 9, 13]. Several explanations can be postulated: there was a higher prevalence of women participants than men with SFA intake over 7% of total dietary energy intake (about 30% in women vs. 20% in men) in the present study; variability in dietary estimation caused by chance eating out may have been higher in men than in women because the proportion of men in full time work was higher than in women; the fact that a higher prevalence of current smoking and alcohol drinking in men than in women could have resulted in some dilution of the SFA effect on CHD mortality in men. In the present study, the possibility that the dietary survey was less valid in men than in women because women were more likely to purchase and prepare food may not be applied because we estimated nutrient intakes of each household member by dividing household intake data of the NNSJ90 conducted in 1990 proportionally using average intakes by sex and age groups calculated for NNSJ95.

Here, we did not find any associations of total dietary fat, PUFA and cholesterol intake with CHD mortality. A lack of these associations is consistent with most previous studies [1, 3, 7, 8, 10, 13-17]. Among the fatty acids that make up the total in the diet, only SFA and trans fatty acids raise

Table 1. Baseline Characteristics by Quintile of Saturated Fatty Acid Intake in 3,254 men--NIPPON DATA90, 1990-2005

SFA range (%kcal)	1.2-4.7	4.7-5.5	5.5-6.2	6.2-7.0	7.0-13.0	Age-adjusted trend P
N	651	650	657	649	647	
CHD case (subtotal=42)	16	8	6	7	5	0.28
Age (y)*	59.2±12.2	55.4±12.7	52.6±13.2	49.5±12.7	47.4±13.3	<0.001*
Total energy (kcal)	2293±18	2308±18	2356±18	2344±18	2309±18	0.25
PUFA (%kcal)	4.9±0.05	5.4±0.05	5.7±0.05	5.9±0.05	6.1±0.05	<0.001
Vegetables (g/1000kcal)	542±3.5	539±3.4	532±3.4	522±3.5	504±3.5	<0.001
Fruits (g/1000kcal)	45.3±1.5	52.6±1.4	53.7±1.4	53.5±1.5	55.0±1.5	<0.001
Fish (g/1000kcal)	59.6±1.0	57.2±1.0	55.9±0.9	53.4±1.0	49.7±1.0	<0.001
Meats (g/1000kcal)	18.7±10.8	25.6±12.3	30.1±13.5	35.9±13.7	42.3±17.8	<0.001
Eggs (g/1000kcal)	15.2±0.4	18.1±0.4	20.2±0.4	21.6±0.4	23.0±0.4	<0.001
BMI (kg/m^2)	23.0±0.1	23.0±0.1	23.0±0.1	22.9±0.1	22.9±0.1	0.22
TCH (mg/dl)	193.7±1.5	195.4±1.5	199.4±1.5	200.5±1.5	203.0±1.5	<0.001
HDL (mg/dl)	50.8±0.6	50.1±0.6	49.3±0.6	50.2±0.6	51.4±0.6	0.55
nonHDL (mg/dl)	142.9±1.6	145.3±1.6	150.1±1.5	150.3±1.6	151.6±1.6	<0.001
Hypertension (%)	58.5	52.3	49.0	42.7	37.9	0.003
Diabetes (%)	8.6	7.4	8.1	7.9	4.5	0.97
Smoker (%)	56.1	52.6	53.4	57.6	56.6	0.08
Drinker (%)	60.7	61.4	59.5	57.5	53.3	<0.001

Baseline characteristics in men by quintile of SFA intake are shown. *Age data are shown as the mean±SD. Continuous variables except for age, are age-adjusted data obtained by analysis of covariance and are shown as the mean±SE. Prevalence is shown as a %. To obtain the trend P for age, and the age-adjusted trend P for other variables, the "contrast" option for analysis of variance or covariance was used for continuous variables, and logistic analysis for prevalence variables. BMI=body mass index, CHD=coronary heart disease, HDL= serum high-density lipoprotein cholesterol concentration, nonHDL=serum nonHDL cholesterol concentration, SFA=saturated fatty acids intake, TCH=serum total cholesterol concentration.

Table 2. Baseline Characteristics by Quintile of Saturated Fatty Acid Intake in 4,565 Women--NIPPON DATA90, 1990-2005

	1.4-5.2	5.2-6.1	6.1-6.8	6.8-7.7	7.7-13.8	Age-adjusted trend P
N	914	910	909	922	910	
CHD case (subtotal=30)	8	7	3	4	8	0.02
Age (y)*	61.8±12.2	55.3±5.2	52.3±13.5	48.4±12.8	44.9±11.9	<0.001*
Total energy (kcal)	1836±12	1862±12	1881±12	1884±12	1861±12	0.08
PUFA (%kcal)	5.2±0.05	5.9±0.04	6.2±0.04	6.5±0.04	6.6±0.05	<0.001
Vegetables (g/1000kcal)	535±2.9	528±2.8	523±2.8	510±2.8	496±2.9	<0.001
Fruits (g/1000kcal)	76.2±1.9	82.3±1.8	83.0±1.8	85.2±1.8	85.5±1.9	<0.001
Fish (g/1000kcal)	58.4±0.8	54.5±0.8	53.6±0.8	51.1±0.8	47.7±0.8	<0.001
Meats (g/1000kcal)	18.5±0.5	25.0±0.4	28.9±0.4	33.6±0.4	40.5±0.5	<0.001
Eggs (g/1000kcal)	16.5±0.3	19.6±0.3	21.5±0.3	23.1±0.3	25.1±0.3	<0.001
BMI (kg/m^2)	23.3±0.1	23.1±0.1	22.9±0.1	22.7±0.1	22.2±0.1	<0.001
TCH (mg/dl)	199.0±1.3	204.8±1.3	208.6±1.3	208.9±1.3	211.1±1.3	<0.001
HDL (mg/dl)	54.0±0.5	55.9±0.5	56.6±0.5	57.4±0.5	60.0±0.5	<0.001
nonHDL (mg/dl)	145.0±1.3	148.9±1.3	152.0±1.3	151.4±1.3	151.1±1.3	<0.001
Hypertension (%)	57.0	48.5	40.3	33.0	24.2	<0.001
Diabetes (%)	5.9	5.2	4.1	2.9	2.3	0.16
Smoker (%)	7.2	7.8	8.7	9.4	12.5	0.003
Drinker (%)	4.4	5.9	6.4	7.8	7.6	0.61

Baseline characteristics in women by quintile of SFA intake are shown. *Age data are shown in mean±SD. Continuous variables except for age, are age-adjusted data obtained by analysis of covariance and are shown as the mean±SE. Prevalence is shown as a %. To obtain the trend P for age, and the age-adjusted trend P for other variables, the "contrast" option for analysis of variance or covariance was used for continuous variables, and logistic analysis for prevalence variables. BMI=body mass index, CHD=coronary heart disease, HDL= serum high-density lipoprotein cholesterol concentration, nonHDL=serum nonHDL cholesterol concentration, SFA=saturated fatty acids intake, TCH=serum total cholesterol concentration.

Table 3. SFA, Total Fat, Polyunsaturated Fatty Acids, Cholesterol Intake and Coronary Heart Disease Mortality in Men and Women

	Men			Women		
	HR	95% CI	P	HR	95% CI	P
SFA (%kcal) (/quintile)						
Model 1	0.90	0.72-1.13		1.38	1.06-1.78	0.016
Model 2	0.89	0.71-1.11	0.300	1.41	1.09-1.84	0.010
Model 3	0.92	0.73-1.16	0.460	1.34	1.02-1.74	0.034
Model 4 (SFA >7% vs ≤ 7%)	0.84	0.32-2.17	0.712	2.59	1.19-5.63	0.016
PUFA (%kcal) (/quintile)						
Model 1	0.95	0.76-1.17	0.604	1.01	0.78-1.30	0.966
Model 2	0.95	0.76-1.17	0.620	0.99	0.77-1.28	0.950
Model 3	0.95	0.77-1.18	0.640	1.00	0.77-1.29	0.974
Total FA (%kcal) (/quintile)						
Model 1	0.89	0.71-1.12	0.329	1.29	0.99-1.67	0.057
Model 2	0.88	0.70-1.12	0.282	1.28	0.99-1.67	0.062
Model 3	0.91	0.71-1.15	0.422	1.24	0.95-1.63	0.110
Dietary cholesterol(mg/1000kcal) (/quintile)						
Model 1	0.93	0.75-1.15	0.482	1.01	0.79-1.30	0.927
Model 2	0.93	0.75-1.15	0.493	1.03	0.80-1.32	0.852
Model 3	0.93	0.74-1.17	0.511	1.09	0.83-1.42	0.544

The multivariate adjusted hazards ratio for coronary heart disease mortality in women was calculated using a Cox's proportional hazards model. Model 1 included age to obtain the hazards ratio for *one increment in quintile of SFA intake*. In addition to age, model 2 included hypertension, diabetes, BMI (<18.5, 18.5-25, 25-30 and >30 kg/m²; 18.5-25 served as a reference), smoking (never-smoked; ex-smoker; current smoker; never-smoked served as a reference), and drinking (never-drinker; ex-drinker; current drinker; never-drinker served as a reference). Finally, in model 3, intake of vegetables, fruit, and fish (g/1000kcal) were added to model 2.

LDL; serum LDL concentrations are independent of intake of total fatty acids. Thus, ATP III recommends that it is not necessary to restrict total fatty acids intake to reduce LDL, provided that SFA are reduced to the target level [28]. Possible confounding effects of trans fatty acids may also be related to the lack of association of PUFA intake and CHD mortality in the present study [29, 30]. Some dilution effects inherent in nutritional studies with a long follow-up period, which will be discussed later, should also be pointed out [29].

The strengths of our study include its prospective design and the follow-up of a randomly selected sample from the general population of Japan with a high response rate (76.5 %). Furthermore, there have been no previous large-scale studies using food intake surveys with weighed food records. Since the study includes men and women with a broad range of ages, findings are likely to be generalizable to middle-aged and elderly Japanese.

As in any long-term follow-up study, however, there are some weaknesses. First, we did not have individual nutritional data, but rather estimated the nutrient intakes of each household member by dividing household intake data of the NNSJ90 conducted in 1990 proportionally using average intakes by sex and age groups calculated for NNSJ95 [23]. Familial resemblance in nutrient intake has been reported in spouses, and also in parents and their children [31-33], and we think that the proportional distribution method used in this study is appropriate for most households. Second, the major results of the present study were based on a relatively small number of CHD deaths in men and women. Third, becausethe follow-up period of our study was relatively long, and dietary exposure tends to change over time, misclassification of dietary exposure is thought to increase over time [29]. Repeated diet assessment wouldhave been better. Fourth, there may have been some other confounding dietary factors [29, 30]. Although we adjusted for vegetable and fruit intake in our analyses, other nutrients such as trans fatty acids should be included in future studies. All the above listed possible limitations could have resulted in dilution of the associations between exposures and CHD mortality. Thus, we might able to make positive associations between exposures and outcome.

In conclusion, SFA intake was positively associated with CHD mortality independent of confounders in women, but not in men.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

hensive Research on Aging and Health [H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, H19-Chouju-Ippan-014] and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus [H22-Jyunkankitou-Seisyu- Sitei-017]).

REFERENCES

[1]   Jakobsen MU, Overvad K, Dyerberg J, SchrollM, Heitmann BL. Dietary fat and risk of coronary heart disease: possible effect modification by gender and age. Am J Epidemiol 2004; 160: 141-9.

[2]   Keys A, Menotti A, Karvonen MJ, *et al.* The diet and 15-year death rate in the Seven Countries Study. Am J Epidemiol 1986; 124: 903-15.

[3]   Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: Lipid research clinics prevalence follow-up study. J Clin Epidemiol 1996; 49: 211-6.

[4]   Boniface DR, Tefft ME. Dietary fats and 16-year coronary heart disease mortality in a cohort of men and women in Great Britain. Eur J Clin Nutr 2002; 56: 786-92.

[5]   Kushi LH, Lew RA, Stare FJ, *et al.* Diet and 20-year mortality from coronary heart disease: The Ireland-Boston Diet-Heart Study. N Engl J Med 1985; 312: 811-8.

[6]   Goldbourt U, Yaari S, Medalie JH. Factors predictive of long-term coronary heart disease mortality among 10,059 male Israeli civil servants and municipal employees: a 23-year mortality follow-up in the Israeli ischemic heart disease study. Cardiology 1993; 82: 100-21.

[7]   Xu J, Eilat-Adar S, Loria C, *et al.* Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. Am J Clin Nutr 2006; 84: 894-902.

[8]   Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R Jr, Cordero E, Rodriguez M. Relationship of dietary intake to subsequent coronary heart disease incidence: the Puerto Rico Heart Health Program. Am J Clin Nutr 1980; 33: 1818-27.

[9]   Pietinen P, Ascherio A, Korhonen P, *et al.* Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: The Alpha-Tocopherol, Beta-carotene cancer prevention study. Am J Epidemiol 1997; 145: 876-87.

[10]   Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. Am J Epidemiol 2005; 161: 672-9.

[11]   Shekelle RB, Shryock AM, Paul O, Shryock AM, Liu S, Lepper M. Diet, serum cholesterol, and death from coronary heart disease: the Western electric study. N Engl J Med 1981; 304: 65-70.

[12]   Yamagishi K, Iso H, Yatsuya H, *et al.* Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan collaborative cohort study for evaluation of cancer risk (JACC) Study. Am J Clin Nutr 2010; 92: 759-65.

[13]   Hu FB, Stampfer MJ, Manson JE, *et al.* Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997; 337: 1491-9.

[14]   McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. Am J Epidemiol 1984; 119: 667-76.

[15]   Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J 3rd. Dietary lipid predictors of coronary heart disease in men. The Framingham Study. Arch Intern Med 1991; 151: 1181-7.

[16]   Kromhout D, De Lezenne Coulander C. Diet, prevalence and 10-year mortality from coronary heart disease in 871 middle-aged men: the Zutphen Study. Am J Epidemiol 1984; 119: 733-41.

[17]   Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. BMJ 1996; 313: 84-90.

[18]   Ueshima H, Iida M, Shimamoto T, *et al.* Dietary intake and serum total cholesterol level: their relationship to different lifestyles in several Japanese populations. Circulation 1982; 66: 519-26.

[19]   Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Ueshima H, The NIPPON DATA90 Research Group: The inverse relationship between serum high-density lipoprotein cholesterol and all-cause mortality in a 9.6-year follow up study in the Japanese general population. Atherosclerosis 2006; 184: 143-150.

[20]   Nakamura K, Okamura T, Hayakawa T, *et al.* Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. Circ J 2006; 70: 954-959.

[21]   Ueshima H, Choudhury SR, Okayama A, *et al.* Cigarette smoking as a risk factor for stroke death in Japan. NIPPON DATA80. Stroke 2004; 35: 1836-41.

[22]   Nakamura Y, Yamamoto T, Okamura T, *et al.* Combined Cardio-vascular Risk Factors and Outcome: NIPPON DATA80, 1980-1994. Circ J 2006; 70: 960-964.

[23]   Okuda N, Miura K, Yoshita K, *et al.* Integration of data from NIP-PON DATA80/90 and National Nutrition Survey in Japan: for co-hort studies of representative Japanese on nutrition. J Epidemiol 2010; 20; S506-14.

[24]   Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US cholesterol reference method laboratory net-work. J Atheroscler Thromb 2003; 10: 145-53.

[25]   Keys A, Anderson JT, Grande F. Prediction of serum-cholesterol responses of man to changes in fats in the diet. Lancet1957; 273:959-66.

[26]   Hegsted DM, McGandy RB, Myers ML, Stare FJ. Quantitative effects of dietary fat on serum cholesterol in man. Am J Clin Nutr 1965; 17: 281-95.

[27]   Hegsted DM, Ausman LM, Johnson JA, Dallal GE. Dietary fat and serum lipids: an evaluation of the experimental data. Am J Clin Nutr 1993; 57: 875-83.

[28]   Third Report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circu-lation 2002; 106: 3143-421.

[29]   Willett W. Nutritional epidemiology. 2nd ed. Oxford, United King-dom: Oxford University Press, 1998.

[30]   Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr 2001; 20: 5-19.

[31]   Kolonel LN, Lee J. Husband-wife correspondence in smoking, drinking, and dietary habits. Am J Clin Nutr 1981; 34: 99-104.

[32]   Perusse L, Tremblay A, Leblanc C, *et al.* Familial resemblance in energy intake: contribution of genetic and environmental factors. Am J Clin Nutr 1988; 47: 629-35.

[33]   Sasaki S, Tsuji T. Influence of co-habitation on a family line re-semblance in nutrient and food-group intake among three genera-tions of Japanese Women. Jpn J Nutr Diet 2000; 5: 195-206.

(5) 日本人の一般集団における乳製品の摂取と循環器疾患死亡：NIPPON DATA80

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【背景】
　近年、牛乳・乳製品の摂取と循環器疾患との負の関連が西洋諸国の研究で報告されている。本研究では、日本における牛乳・乳製品の摂取と循環器疾患死亡との関連について検討した。

【方法】
　1980年に日本全体の300地区で実施した国民栄養調査の対象者のうち30歳以上の男女を24年間追跡した。牛乳・乳製品摂取量の3分位間の死亡リスクをコックスの比例ハザードモデルにより高摂取群を基準として算出した。また、摂取量1日100g増加あたりのハザード比も算出した。

【結果】
　対象者9,243人の24年間の追跡期間における循環器疾患死亡は893人で、そのうち心疾患死亡が174人、脳血管疾患死亡が417人であった。女性において、低摂取群の循環器疾患死亡、心疾患死亡、脳血管疾患死亡のハザード比は年齢、BMI、喫煙習慣、飲酒習慣、糖尿病歴、降圧剤服薬、職業区分および総エネルギー摂取量を調整した場合それぞれ1.27（95%信頼区間：0.99-1.58；トレンド p=0.045）、1.67（0.99-2.80；p=0.02）、