SUPPLEMENTAL MATERIAL

Appendix

The NIPPON DATA80 Research Group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-Chairperson: Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo).

Research members: Shigeyuki Saitoh (Department of 2nd Internal Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Iwate), Atsushi Hozawa (Department of Public Health, Yamagata University Graduate School of Medicine, Yamagata), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima), Yosikazu Nakamura (Department of Public Health, Jichi Medical University, Shimotsuke, Tochigi), Yasuhiro Matsumura (Faculty of Healthcare, Kiryu University, Midori City, Gunma), Nobuo Nishi (Project for the National Health and Nutrition Survey, National Institute of Health and Nutrition, Tokyo), Nagako Okuda (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo), Toru Izumi (Faculty of Medicine, Kitasato

University, Sagamihara, Kanagawa), Toshiyuki Ojima (Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka), Koji Tamakoshi (Department of Public Health and Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya, Aichi), Hideaki Nakagawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Katsuyuki Miura, Takayoshi Ohkubo, Yoshikuni Kita, Aya Kadota (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Yasuyuki Nakamura (Cardiovascular Epidemiology, Kyoto Women's University, Kyoto), Katsushi Yoshita (Osaka City University Graduate School of human life science, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima), and Yutaka Kiyohara (Department of Environmental Medicine, Kyushu University, Fukuoka).

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ORIGINAL ARTICLE

Hypertension and life expectancy among Japanese: NIPPON DATA80

Tanvir Chowdhury Turin[1,2], Yoshitaka Murakami[3], Katsuyuki Miura[2], Nahid Rumana[2], Yoshikuni Kita[2], Takehito Hayakawa[4], Tomonori Okamura[5], Akira Okayama[6], Hirotsugu Ueshima[2,7] and of the NIPPON DATA80/90 Research Group[8]

Life expectancy (LE) is a measure that describes the health status of a population. The few published studies that have examined the impact of hypertension on LE were predominantly performed in Western populations. The effect of hypertension on LE has not been reported in an Asian population. Thus, we examined the impact of hypertension on LE in the Japanese population, which has the highest LE worldwide. The abridged life table method was applied to calculate the LEs of both normotensive and hypertensive men and women aged 40–85 years. Hypertensive participants were categorized as having either stage 1 or stage 2 hypertension. Age-specific mortality rates across different groups were estimated using the person–year method based on the follow-up data from a representative Japanese population in a national survey (NIPPON DATA80). The proportion of hypertensive patients in the baseline survey was 50.5% for men and 41.4% for women. The LE of 40-year-old men and women was 41.7 years and 48.7 years, respectively, in normotensive participants and 39.5 and 45.8 years, respectively, in hypertensive participants. The LE difference between normotensive and hypertensive participants was 2.2 years for men and 2.9 years for women. LE decreased with increasing stages of hypertension. Similar patterns of LE, with respect to blood pressure (BP) status, were observed in all index ages and for both genders. At the population level, hypertension leads to decreased LE and affects both genders similarly. Our findings highlight the importance of preventing high BP and the consequences of hypertension in Japanese population.
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Keywords: blood pressure; Japan; life expectancy; middle age; mortality

INTRODUCTION

Studies have shown that hypertension, or high blood pressure (BP), is quite prevalent worldwide[1] and is a major risk factor for morbidity and mortality in young, middle-aged and elderly individuals of both genders.[2–4] Moreover, hypertension is also closely linked to the aging process, as the prevalence and the risk of hypertension increase with age.[5,6] A similar influence of age is also found with regard to mortality.[7,8] The measure life expectancy (LE), which is a comprehensive estimate of a given population's health status, provides a useful and direct means to communicate disease burden and can be used as a universal measure of health in a population. This information can be used to prioritize planning and policy making for the detection, treatment and control of various health conditions.

There are few published studies that have investigated the impact of hypertension on LE.[9–11] Although the impact of hypertension on premature death and LE has been estimated in Western populations, the effect of hypertension on LE has not been reported in Asian populations, including the Japanese population. This information will be of importance because it is unclear how hypertension affects LE in the Japanese population, which currently has the highest longevity worldwide. The present study examined the LE of a representative sample of Japanese population in which hypertension status varied. This is the first population-based Japanese study of LE for people with and without hypertension.

METHODS

Data source

The present study analyzed data from NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged), which was collected from a baseline survey performed in 1980. The details of this cohort have been reported elsewhere.[3,12,13] In brief, 300 areas were selected by stratified random sampling from all over Japan, and

[1]Department of Medicine, University of Calgary, Calgary, Alberta, Canada; [2]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; [3]Department of Medical Statistics, Shiga University of Medical Science, Otsu, Japan; [4]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan; [5]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan; [6]The First Institute for Health Promotion and Health Care, Tokyo, Japan and [7]Life-style Related Disease Prevention Center, Shiga University of Medical Science, Otsu, Japan
[8]Members of the NIPPON DATA80/90 Research Group are listed in the Appendix.
Correspondence: Dr TC Turin, Department of Medicine, University of Calgary, Calgary, Alberta, Canada.
E-mail: turin.chowdhury@ucalgary.ca or dr.turin@gmail.com
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a sample of residents aged 30 years or older in these areas was invited to participate. A total of 10546 residents (4639 men and 5907 women) participated in the survey (response rate: 76.6%). The baseline surveys were carried out at local public health centers. The participants were followed for 24 years, until November 2004.

To identify death events among the cohort, we used national vital statistics. In accordance with Japan's Family Registration Law, all death certificates issued by the medical doctors are to be forwarded to the Ministry of Health, Labor and Welfare via the public health centers in the respective participant's area of residency. We confirmed death in each area by computer matching of vital statistics data using area, sex, date of birth and date of death as key codes. Permission to use the national vital statistics was obtained from the Management and Coordination Agency of the Government of Japan. In the present study, we excluded participants who had missing information at baseline or who were lost to follow-up ($n=941$). Thus, the final sample consisted of 9605 participants (4228 men and 5377 women). There were no significant differences between the participants who were lost to follow-up and those who were included in the current study in terms of several risk factors. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (no. 12-18 2000).

BP measurement and categories

Baseline BP was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as systolic BP $\geqslant$ 140 mm Hg and/or diastolic BP $\geqslant$ 90 mm Hg and/or taking antihypertensive medication. Participants with BP $<$ 140 mm Hg and diastolic BP $<$ 90 mm Hg were defined as normotensive. We further categorized the hypertensive participants, without regard to the use of antihypertensive medication, according to the classification by the JNC-7[14] as follows: stage 1 hypertension, systolic BP 140–159 mm Hg and/or diastolic BP 90–99 mm Hg, or stage 2 hypertension, systolic BP $\geqslant$ 160 mm Hg and/or diastolic BP $\geqslant$ 100 mm Hg. We decided not to consider treatment of hypertension in the categorization of our analyses because we wanted to evaluate the effect of increased BP levels, which can also arise in hypertensive patients under treatment. When the systolic and diastolic pressures fell into different categories, the higher category was selected for the purposes of classification.

Statistical analysis

Age-specific mortality rates for the cohort participants were calculated using the person–year method,[15] and age was considered in the timescale with synchronization with the follow-up. The age bands used in this calculation were defined in 5-year increments. The age categories began at age 40–44 years, and the highest age category was set at age 85 years and over. The abridged life table method was used to calculate life expectancies using age-specific mortality rates. The fraction of the last age interval of life[13,16] was used to construct an abridged life table. Those fractions were calculated from a complete life table for the year 1990 in Japan.[13] Each LE was calculated from age 40 to age 85 in 5-year intervals. We also calculated 95% confidence intervals for LE in each age group. All of the statistical analyses were performed using SAS release 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the basic characteristics of the participants with different hypertension statuses in the baseline survey. The proportion of hypertensive participants in the baseline survey was 50.5% for men and 41.4% for women. In men, 13.5% of the participants had stage 1 hypertension and 36.2% of the participants had stage 2 hypertension. In women, the respective proportions were 15.0% and 25.1%. Hypertensive patients were generally older and had higher mean plasma glucose and higher total blood cholesterol levels. This difference was observed in both men and women.

The overall LE of the 40-year-old participants, regardless of BP status, was 40.4 years for men and 47.0 years for women. These LE values were higher than the LEs in the complete life table for Japan from 1990. In that table, LE was 37.5 years for men and 42.9 years for women.[17] The observed differences were consistent across all age groups in both genders. Table 2 shows the LE among the participants with different BP statuses from age 40 to 85 years and over. LEs in 40-year-old men and women were 41.7 years and 48.7 years, respectively, in normotensive participants and 39.5 years and 45.8 years, respectively, in hypertensive participants. Thus, the LEs of 40-year-old normotensive participants were greater than those of hypertensive participants. Similar patterns of LE with respect to BP status were observed in all the age groups. The LEs in men with stage 1 hypertension were greater than those of men with stage 2 hypertension. Similar results were observed in women. The longer LE for participants with stage 1 hypertension in comparison with participants with stage 2 hypertension was observed across all age indices for both genders.

DISCUSSION

In this study, LE was estimated for Japanese men and women with and without diagnosed hypertension. The results attribute a significant loss of LE to hypertension. To the best of our knowledge, this is the first study to report the effect of the presence or absence of hypertension on LE in a Japanese population. We observed that the LE of hypertensive men and women was 2–3 years shorter than the LE of normotensive men and women, especially in the middle-aged categories. Increases in hypertension stage also inversely affected LE.

Similar to our observation, Loukine *et al.*[11] recently reported a 2–3 years difference in LE associated with hypertension in a Canadian population. They estimated the LE in 40-year-old men and women to be 41.9 years and 45.8 years, respectively, in normotensive subjects and 38.8 years and 43.7 years, respectively, in hypertensive subjects. After estimating the effect of hypertension on LE in an eastern Finland population, Kiiskinen *et al.*[10] reported that LE was shortened by 2.7 years in hypertensive men and 2.2 years in hypertensive women. Franco *et al.*,[9] studying the participants in the Framingham Heart Study, reported that the differences in LE between 50-year-old normotensive and hypertensive subjects were 5.1 years in men and 4.9 years in women. They estimated the LE in 50-year-old men and women to be 29.7 years and 34.3 years, respectively, in normotensive subjects and 24.6 years and 29.4 years, respectively, in hypertensive subjects. The effect of hypertension on LE in the Framingham Heart Study was much greater than in our Japanese study, the Canadian study and the Finish study. We also observed that the LE for women is higher than that for men, a direct result of higher mortality among men. A similar pattern was observed for the populations both with and without hypertension. Similar observations were reported for the Canadian population, for both subjects with and without hypertension. We observed that the reduction in LE was larger for men than for women. The estimates from other studies were also consistent: the decrease in LE was greater for men than for women.[10,11] It is important to note that direct comparability with our results was hampered by differences in methodology, data used, reporting year and characteristics of the populations studied. Among the subcategories of hypertension, stage 1 and stage 2, decreases in the LE of 40-year-olds were observed as the hypertension grade increased. This tendency was less pronounced when we measured LE in the older-age groups. This finding might be attributed to the small sample size of the older-age group.

Regarding the effect of hypertension on the LE of the elderly population, we observed that the presence of hypertension was associated with reduced LE. Severe hypertension led to reductions in LE. However, the overall impact of milder hypertension was much

Table 1 The basic characteristics of Japanese with different hypertension status in the baseline, NIPPON DATA80, Japan

		Blood pressure categories			
				Hypertension	
Gender	*Variables*	*No hypertension*	*Hypertension*	*Stage 1*	*Stage 2*
Men	Age, years (s.d.)	45.9 (11.9)	55.4 (12.9)	56.6 (13.2)	54.8 (12.7)
	BMI, kgm^{-2} (s.d.)	22.1 (2.8)	22.9 (2.9)	22.3 (2.7)	23.1 (3.0)
	Height, cm (s.d.)	163.5 (19.5)	161.5 (19.3)	162.1 (35.8)	161.3 (6.5)
	Weight, kg (s.d.)	59.0 (19.5)	59.6 (9.5)	56.8 (9.0)	60.3 (9.5)
	Plasma glucose, $mgdl^{-1}$ (s.d.)	98.3 (29.2)	106.4 (35.3)	107.3 (37.0)	105.8 (34.4)
	Total cholesterol, $mgdl^{-1}$ (s.d.)	183.9 (31.9)	188.1 (33.7)	183.9 (31.7)	189.7 (34.1)
	Serum creatinine, $mgdl^{-1}$ (s.d.)	1.0 (0.1)	1.1 (0.3)	1.1 (0.2)	1.1 (0.3)
	Smoking, *n* (%)				
	Never smoker	357 (17.1)	417 (19.5)	95 (16.7)	315 (20.6)
	Current smoker	1388 (66.3)	1268 (59.4)	357 (62.7)	896 (58.5)
	Ex-smoker	346 (16.5)	445 (20.8)	116 (20.4)	316 (20.6)
	Unknown	2 (0.1)	5 (0.2)	1 (0.2)	4 (0.3)
	Drinking, *n* (%)				
	Never drinker	467 (22.3)	377 (17.7)	125 (22.0)	249 (16.3)
	Current drinker	1520 (72.6)	1613 (75.6)	403 (70.8)	1187 (77.5)
	Ex-drinker	104 (5.0)	141 (6.6)	41 (7.2)	91 (5.9)
	Unknown	2 (0.1)	4 (0.2)	0 (0.0)	4 (0.3)
Women	Age, years (s.d.)	45.8 (11.7)	58.8 (12.1)	58.7 (12.0)	57.9 (12.3)
	BMI, kgm^{-2} (s.d.)	22.2 (3.1)	23.8 (3.6)	23.3 (3.4)	24.0 (3.7)
	Height, cm (s.d.)	151.2 (5.8)	148.3 (6.2)	148.2 (6.0)	148.4 (6.2)
	Weight, kg (s.d.)	50.8 (7.7)	52.4 (9.1)	51.2 (8.6)	53.1 (9.2)
	Plasma glucose, $mgdl^{-1}$ (s.d.)	96.7 (24.3)	107.0 (33.4)	108.2 (35.7)	106.4 (32.4)
	Total cholesterol, $mgdl^{-1}$ (s.d.)	185.5 (32.7)	199.6 (34.3)	197.7 (33.9)	200.3 (34.6)
	Serum creatinine, $mgdl^{-1}$ (s.d.)	0.8 (0.1)	0.9 (0.2)	0.9 (0.3)	0.9 (0.2)
	Smoking, *n* (%)				
	Never smoker	2801 (89.2)	1968 (88.4)	705 (87.6)	1201 (89.0)
	Current smoker	280 (8.9)	194 (8.7)	76 (9.4)	113 (8.4)
	Ex-smoker	56 (1.8)	63 (2.8)	23 (2.9)	36 (1.7)
	Unknown	5 (0.2)	1 (0.0)	1 (0.1)	0 (0.0)
	Drinking, *n* (%)				
	Never drinker	2405 (76.3)	1818 (81.7)	674 (83.7)	1084 (80.3)
	Current drinker	698 (22.2)	363 (16.3)	118 (14.7)	236 (17.5)
	Ex-drinker	43 (1.4)	40 (1.8)	13 (1.6)	25 (1.6)
	Unknown	5 (0.2)	5 (0.2)	0 (0.0)	5 (0.4)

Abbreviations: BMI, body mass index; NIPPON DATA80: National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged; s.d., standard deviation.

more limited. Given the aging of the Japanese population and that of the worldwide population, these LE findings reemphasize the importance of hypertension control, even in the elderly.

Our finding is generalizable to the Japanese population by virtue of the cohort we used for the LE estimation. The NIPPON DATA80 cohort was initially selected by stratified random sampling throughout Japan as part of a national survey. Comparing our results with the complete life table for the same period in Japan,[17] the overall LE of 40-year-old participants, regardless of BP status, was 40.4 years for men and 47.0 years for women. These were higher than the LEs from the complete life table in Japan in 1990, which were 37.5 years for men and 42.9 years for women. The LEs that we measured were greater than those from the complete life table. This difference might be attributed to the overall healthier status of our cohort. In the baseline survey, people with health problems, such as residents of long-term care facilities, could not participate in the survey. This exclusion criterion may have caused age-specific mortality rates to be lower than population as a whole, which could have resulted in the LE differences observed in this study. The stable population in the final age interval (age 85 and over) was calculated as the number of survivors 85 years or older divided by their death rate. Although this is an accepted way to analyze the final age interval for LE calculations, it may overestimate LE.[13,18] This overestimation also influences the difference between our results and those from the complete life table.

Possible misclassifications of long-term BP categories might also influence our results. The classification of hypertension status was made using only the information obtained from the baseline survey, with the assumption that individuals' hypertension status did not change during the follow-up period. This assumption would be violated if any normotensive participant became hypertensive with ageing. It is not possible to precisely ascertain how much change in hypertensive status occurred during the 24-year period. The influence of this misclassification might attenuate the LE differences observed among the groups, and misclassification might render our estimates more conservative. It should also be recognized that all of the LE differences observed in this study were not caused by hypertension

Table 2 Life expectancies of Japanese with different blood pressure status from NIPPON DATA80, 24-year follow-up, 1980–1999, Japan

		Blood pressure categories							
						Hypertension			
		No hypertension		*Hypertension*		*Stage 1*		*Stage 2*	
Gender	*Index age (years)*	*LE*	*95%CI*	*LE*	*95%CI*	*LE*	*95%CI*	*LE*	*95%CI*
Men									
	40	41.7	(41.0, 42.5)	39.5	(38.8, 40.3)	40.6	(39.2, 42.0)	39.2	(38.3, 40.1)
	45	36.9	(36.1, 37.7)	34.8	(34.1, 35.5)	35.6	(34.2, 37.0)	34.6	(33.8, 35.4)
	50	32.3	(31.6, 33.1)	30.5	(29.9, 31.1)	31.3	(30.0, 32.5)	30.3	(29.6, 31.0)
	55	27.8	(27.1, 28.5)	26.0	(25.4, 26.5)	26.9	(25.8, 28.1)	25.7	(25.0, 26.4)
	60	23.4	(22.7, 24.2)	21.9	(21.4, 22.4)	22.9	(21.9, 24.0)	21.6	(21.0, 22.2)
	65	19.4	(18.7, 20.1)	17.9	(17.4, 18.4)	18.6	(17.7, 19.6)	17.7	(17.1, 18.2)
	70	15.6	(14.9, 16.2)	14.2	(13.7, 14.6)	15.1	(14.3, 16.0)	13.9	(13.3, 14.4)
	75	12.2	(11.6, 12.8)	11.0	(10.6, 11.4)	11.7	(11.0, 12.5)	10.7	(10.2, 11.2)
	80	9.2	(8.7, 9.8)	8.5	(8.2, 8.9)	9.2	(8.6, 9.8)	8.3	(7.9, 8.7)
	85	7.2	(6.8, 7.7)	6.6	(6.4, 6.8)	7.1	(6.7, 7.5)	6.4	(6.2, 6.7)
Women									
	40	48.7	(48.0, 49.3)	45.8	(45.0, 46.6)	47.0	(45.9, 48.2)	44.9	(43.9, 46.0)
	45	43.9	(43.2, 44.5)	41.0	(40.3, 41.7)	42.0	(40.9, 43.2)	40.2	(39.3, 41.2)
	50	39.1	(38.5, 39.7)	36.5	(35.9, 37.1)	37.3	(36.3, 38.3)	35.9	(35.1, 36.7)
	55	34.3	(33.7, 35.0)	32.0	(31.4, 32.5)	32.9	(32.0, 33.7)	31.3	(30.5, 32.0)
	60	29.8	(29.2, 30.4)	27.6	(27.1, 28.0)	28.3	(27.5, 29.0)	26.9	(26.2, 27.5)
	65	25.3	(24.7, 25.9)	23.1	(22.7, 23.6)	23.7	(22.9, 24.4)	22.5	(21.9, 23.1)
	70	21.0	(20.4, 21.6)	19.0	(18.6, 19.5)	19.6	(18.9, 20.2)	18.5	(17.9, 19.0)
	75	17.1	(16.5, 17.6)	15.1	(14.7, 15.5)	15.4	(14.8, 16.0)	14.7	(14.2, 15.1)
	80	13.5	(13.0, 14.0)	11.8	(11.4, 12.1)	12.1	(11.6, 12.5)	11.3	(10.9, 11.7)
	85	10.5	(10.1, 11.0)	9.1	(8.9, 9.4)	9.2	(8.7, 9.4)	8.9	(8.6, 9.1)

Abbreviations: CI, confidence intervals; LE, life expectancy; NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged. Hypertension stages are based on blood pressure measurement, irrespective of medication.

status alone; in fact, other factors in addition to hypertension also affected the mortality rate. The LE differences among the hypertension categories result from the hypertensive participants' risk factor profile, not from BP alone. Thus, in addition to hypertension, other factors simultaneously influenced the LE in our population, including smoking habits,[13] diabetes mellitus[19] and dyslipidemia. Alternatively, hypertension is a convenient marker that functions as a surrogate for health risks not controlled for in the analysis.

In conclusion, the LEs of participants with different hypertension statuses were examined using data from a nationwide cohort study in Japan. A gradual decrease in LE was observed when hypertension was present, and the decrease was greater with increasing disease severity in both men and women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

The NIPPON DATA80/90 research group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-Chairperson: NIPPON DATA80: Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo); NIPPON DATA90: Tomonori Okamura (Department of Preventive Medicine and Public Health, Keio University, Tokyo).

Research members: Shigeyuki Saitoh (Department of 2nd Internal Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Iwate), Atsushi Hozawa (Department of Public Health, Yamagata University Graduate School of Medicine, Yamagata), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima), Yosikazu Nakamura (Department of Public Health, Jichi Medical University, Shimotsuke, Tochigi), Yasuhiro Matsumura (Faculty of Health care, Kiryu University, Midori City, Gunma), Nobuo Nishi (Project for the National Health and Nutrition Survey, National Institute of Health and Nutrition, Tokyo), Nagako Okuda (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo), Toru Izumi (Faculty of Medicine, Kitasato University, Sagamihara, Kanagawa), Toshiyuki Ojima (Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka), Koji Tamakoshi (Department of Public Health and Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya, Aichi), Hideaki Nakagawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Katsuyuki Miura, Takayoshi Ohkubo, Yoshikuni Kita, Aya Kadota (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Yasuyuki Nakamura (Cardiovascular Epidemiology, Kyoto Women's University, Kyoto), Katsushi Yoshita (Osaka City University Graduate School of Human Life Science, Osaka), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima), and Yutaka Kiyohara (Department of Environmental Medicine, Kyushu University, Fukuoka).

Original Article

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

Naoyuki Takashima[a,b], Takayoshi Ohkubo[a], Katsuyuki Miura[a], Tomonori Okamura[c], Yoshitaka Murakami[d], Akira Fujiyoshi[a], Shin-ya Nagasawa[a,e], Aya Kadota[a], Yoshikuni Kita[a], Naoko Miyagawa[a], Takashi Hisamatsu[a], Takehito Hayakawa[f], Akira Okayama[g], Hirotsugu Ueshima[a,b], for the NIPPON DATA80 Research Group

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.

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[a]Department of Health Science, [b]Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science, Shiga, [c]Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, [d]Department of Medical Statistics, Shiga University of Medical Science, Shiga, [e]Department of Epidemiology and Public Health, Kanazawa Medical University, Ishikawa, [f]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima and [g]The First Institute for Health Promotion and Healthcare, Japanese Anti-Tuberculosis Association, Tokyo, Japan

Correspondence to Naoyuki Takashima, MD, PhD, Department of Health Science, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan. Tel: +81 77 548 2191; fax: +81 77 543 9732; e-mail: takasima@belle.shiga-med.ac.jp

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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 13 730 people – were recruited by local public health centers and the baseline survey was carried out at these local health centers. A total of 10 546 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 [$pd \times$ (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 182 910 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 100 000 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/m^2)	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, <120/80 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.

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.

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, non-normal 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 significant 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 non-cardiovascular 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.

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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 prehypertension 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 sphygmomanometer.

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

Yasuyuki Nakamura[1,2], Yutaka Kiyohara[3], Nagako Okuda[4], Tomonori Okamura[5], Aya Higashiyama[6], Makoto Watanabe[7], Aya Kadota[8], Shin-ya Nagasawa[2,9], Naoko Miyagawa[2], Takayoshi Ohkubo[2], Yoshikuni Kita[2], Katsuyuki Miura[2], Akira Okayama[4], Hirotsugu Ueshima[2], for the NIPPON DATA Research Group

[1]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan; [2]Department of Health Science, Shiga University of Medical Science, Otsu, Japan; [3]Department of Environmental Medicine, Kyushu University, Fukuoka, Japan; [4]First Institute for Health Promotion and Health Care, Tokyo, Japan; [5]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan; [6]Department of Environmental Medicine, Hyogo Medical School, Nishinomiya, Japan; [7]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan; [8]Department of Epidemiology and Public Health, Osaka Kyoiku University, Osaka, Japan; [9]Department of School Nursing and Health Education, Kanazawa Medical University, Ishikawa, Japan

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 cholesterol 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 Noncommunicable 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

*Address correspondence to this author at the Kyoto Women's University, 35 Imakumano Kitahiyoshi-cho, Higashiyama-ku, Kyoto 605-8501, Japan; Fax/Tel: +81-75-531-2162; E-mail: nakamury@kyoto-wu.ac.jp

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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/m^2; 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/m^2; 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.

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