Systolic Blood Pressure Predicts Cardiovascular Mortality in a Farming but Not in a Fishing Community – A 40-Year Follow up of the Japanese Cohorts of the Seven Countries Study –
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Background: Blood pressure (BP) is a strong determinant of cardiovascular diseases (CVD). The strength of this association in 2 Japanese communities with different intakes of fish was investigated.

Methods and Results: The analysis was carried out in the Japanese cohorts of the Seven Countries Study (Tanushimaru and Ushibuka), which were followed for 40 years. We included 1,006 subjects for whom data on baseline BP and relevant potential confounders were available. Data were analysed using multivariable Cox proportional hazard models. In Tanushimaru men, the systolic BP level was strongly directly related to risk of stroke and CVD mortality, with hazard ratios (HR) of 4.42 (2.02–9.70) for stroke and 3.05 (1.73–3.25) for CVD for BP levels ≥140 mmHg compared to <120 mmHg. In Ushibuka, the HR were 1.74 (0.91–3.32) for stroke mortality and 1.66 (1.01–2.75) for CVD mortality for high vs. low systolic BP. With regard to diastolic BP, the associations with stroke and CVD mortality were similar in Tanushimaru and Ushibuka subjects.

Conclusions: This study showed that the well-known relationship of systolic BP with stroke and CVD mortality was more pronounced in the Japanese farming community than in the fishing community. This brings up the hypothesis that the detrimental effect of raised systolic BP could be attenuated by a high intake of fish. (Circ J 2011; 75: 1890–1896)

Key Words: Blood pressure; Cardiovascular diseases; Epidemiology; Nutrition

The mortality pattern of Japan is characterized by a low mortality rate from coronary heart disease (CHD) and a high rate from stroke.1 In spite of a large decrease in the past decades, stroke is still the major contributor to cardiovascular mortality in the Japanese population.2–4 Elevated blood pressure (BP) is a major contributor to mortality and incident cardiovascular diseases (CVD), especially stroke, in Japan.5,6 In spite of an increasing trend in serum cholesterol in more recent years in Japan, the CHD mortality rates have remained relatively low possibly because the average serum cholesterol level stayed below 5 mmol/L.7 Also the high level of fish intake and consequently the high content of the very long-chain n-3 fatty acids, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), in the Japanese diet, were put forward as an explanation for the low CHD mortality rate.8

Meta-analyses of prospective cohort studies have shown that a small amount of fish lowers the risk of fatal CHD and the incidence of fatal and non-fatal stroke.9,10 Also a modest intake of marine-derived n-3 fatty acids (=250–500 mg/day) was associated with a low risk of CHD mortality in a meta-analysis that included both prospective cohort studies and clinical trials.11 This low level of n-3 fatty acids does not lower BP but a high intake (>3 g/day) does.12,13

In Japan several studies have been carried out comparing farming and fishing villages.14–18 These studies showed that the average level of fish consumption in farming villages was approximately 100 g/day, whereas it was 200–250 g/day in fishing villages. The levels of n-3 fatty acids in blood were higher and platelet aggregation, pulse wave velocity, an indicator of atherosclerosis, and Intima Media Thickness were more favorable in people from the fishing villages.14–18

In the present study, we investigated whether the strength of the well-known graded association between BP and long-term risk of stroke and total CVD mortality differed between a farming and a fishing community. We examined this re-
Methods

Seven Countries Study

The Seven Countries Study is an epidemiologic population-based study that started in the late 1950s. In 16 cohorts including 2 Japanese ones, men aged 40–59 years were enrolled between 1958 and 1964. The cohort of Tanushimaru (n=508, examined in 1958) consisted predominantly of farmers, whereas the cohort of Ushibuka (n=502, examined in 1960) consisted mainly of fishermen. The present analysis includes a total of 1,006 men for whom complete data on baseline BP and major confounders was available.

BP

BP was measured from the right arm by trained physicians at the end of the physical examination using a calibrated mercury sphygmomanometer, with the subject in the supine position, as described in the World Health Organization (WHO) manual, Cardiovascular Survey Methods. The mean of 2 measurements, taken 1 min apart, was computed for both the systolic and the diastolic (phase V) BP. Hypertension was defined as a systolic BP of 140 mmHg or higher, a diastolic BP of 90 mmHg or higher, or both. During the baseline surveys, medication to lower BP was rarely prescribed in Japan and therefore medication use was not included in the definition of hypertension.

Other Baseline Risk Factors

Height and weight were measured once when subjects were in light underwear and were without shoes, and the body mass index (BMI) was calculated. Resting heart rate was calculated from the resting ECG as the average of the rates in lead I and V6. Non-fasting blood samples were drawn and cholesterol was determined in fresh serum after saponification and by color development with ferric ion. A few dried serum samples were sent from Japan to Minneapolis, USA, the coordinating center of the Seven Countries Study. Minneapolis serum cholesterol analyses were conducted according to the Abell–Kendall method, modified by Anderson and Keys. The average serum cholesterol value was higher in Tanushimaru samples than in Minneapolis samples (4.34 vs. 3.96 mmol/L) in 1958. Therefore, the cholesterol values in Tanushimaru, were adjusted to the Minneapolis values by multiplying the result with 0.9089. In 1960 in Ushibuka, the data were in good agreement with those from Minneapolis.

Information about smoking habits and occupation was collected by means of standardized questionnaires. Smoking status was coded into 3 categories: current, former and never cigarette smokers. Occupation was coded into 4 categories: farmers, fishermen, manual workers and professionals including business men and governmental officials. The men were classified according to their habitual job-related physical activity into 3 categories: sedentary, moderate physical work and hard physical work.

Mortality

During 40 years of follow up, the vital status of the men was
continuously monitored and no one was lost to follow up. Information was collected on the different causes of death. In Tanushimaru, the 40-year follow-up period was completed. In Ushibuka, the censor date was September 1999 and the baseline examinations took place between May and July 1960. So, the follow-up period in Ushibuka was 39.3 years.

During the first 25 years of follow up, information about the causes of death was obtained from official death certificates, medical and hospital records, and relatives of the person who died or other witnesses. After 25 years, only death certificates were available. In cases in which multiple causes of death were possible, priority was given to violent death, followed by cancer in an advanced stage, CHD, and stroke, respectively. The final adjudication of the underlying cause of death and the contributory causes was made according to the criteria of the WHO International Classification of Diseases, 8th Revision (ICD-8), by an experienced clinical epidemiologist.

Stroke was defined as ICD-8 codes 430 through 438, and CHD as ICD-8 codes 410 through 414 and 795. Total CVD were defined as diseases of the circulatory system, ICD-8 codes 390 through 458, and 795 when sudden death of cardiac origin was mentioned.

**Statistical Methods**

We computed means and standard deviations for continuous variables and relative frequencies (percentages) for discrete ones. We compared means of both cohorts using the t- or χ² test and a 2-sided P-value of <0.05 was considered statistically significant. BP was classified into 3 categories: <120 mmHg, 120–139 mmHg and ≥140 mmHg for systolic BP and <70, 70–84 and ≥85 mmHg for diastolic BP. Cox proportional hazard analysis was performed for the 2 different cohorts to estimate the strength of associations between BP and 40-year mortality from stroke and total CVD. Hazard ratios were obtained with 95% confidence intervals. In multivariable analysis, we adjusted for age, height, weight, smoking status, physical activity and occupation.
BP and CVD in Japanese Farmers and Fishermen

Ushibuka) and systolic BP (as a continuous variable) was tested by adding the product term to the multivariable models. We did not analyze the association of BP with CHD mortality or mortality from “other CVD” because of the limited number of cases. All statistical analyses were conducted using the SPSS system statistical software (version 17.0).

**Results**

The baseline characteristics of the 2 cohorts are shown in Table 1. Average BMI (22 kg/m²) and serum cholesterol (4 mmol/L) were low in both communities. The prevalence of hypertension was 7% lower in Tanushimaru than in Ushibuka (P=0.02). Most men smoked; 71% in Tanushimaru and 78% in Ushibuka. In Ushibuka, more men had a sedentary job (7% vs. 4% in Tanushimaru; P<0.01). Men from Tanushimaru were mainly farmers (78%) whereas men from Ushibuka were mainly fishermen (65%). The prevalence of CVD (defined as a clinically diagnosed myocardial infarction or stroke) was below 1% in both communities.

Long-term mortality rates for different causes of death in Tanushimaru and Ushibuka cohorts are presented in Table 2. The total CVD and overall mortality were lower in the Tanushimaru than in the Ushibuka cohort, but these differences were not statistically significant. Within the category of CVD mortality, Tanushimaru men had a significantly lower risk of symptomatic heart disease (ICD-8 code 427) than Ushibuka men.

In the Tanushimaru cohort, the risk of stroke and CVD mortality showed a strong and graded relationship with systolic BP (Table 3; Figure A), which remained after adjustment for confounders. Men with a systolic BP of 140 mmHg or higher had a more than 4-fold higher risk of stroke mortality and a 3-fold higher risk of CVD mortality compared with men who had a BP below 120 mmHg. Ushibuka men with a systolic BP of 140 mmHg or higher (but not those with a BP of 120–139 mmHg) had a 1.7-fold higher risk of stroke and CVD mortality (Table 3; Figure A). The interaction between area of residence and systolic BP was statistically significant for stroke (P=0.03) and borderline significant for CVD mortality (P=0.09).

In the subpopulation of Tanushimaru farmers, the 40-year...
Table 4. Diastolic BP and 40-Year Mortality From Stroke and Total CVD in Tanushimaru and Ushibuka

<table>
<thead>
<tr>
<th></th>
<th>Tanushimaru</th>
<th></th>
<th>Ushibuka</th>
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<tbody>
<tr>
<td></td>
<td>&lt;70mmHg</td>
<td>70–84mmHg</td>
<td>≥85mmHg</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td></td>
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<td></td>
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<tr>
<td>No. of events</td>
<td>n=184</td>
<td>n=219</td>
<td>n=105</td>
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<td>HR, model 2**</td>
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<td>2.81 (1.49–5.29)</td>
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<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
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<td>50</td>
<td>37</td>
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<tr>
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<td>2.32 (1.39–3.89)</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1,2.

*Adjusted for age. **Adjusted for age, height, weight, smoking status, physical activity and occupation.

Table 4. Diastolic BP and 40-Year Mortality From Stroke and Total CVD in Tanushimaru and Ushibuka

The associations of systolic BP with 40-year mortality from stroke and CVD differed between the two communities. In the Tanushimaru cohort, a graded relationship was observed and in the Ushibuka cohort, only men with a systolic BP of 140 mmHg or higher had an elevated risk. When the analysis was restricted to the subpopulation of farmers in Tanushimaru, the strong associations of systolic BP with stroke and CVD mortality remained. However, in Ushibuka fishermen, the associations of BP with stroke and CVD mortality disappeared. Remarkably, this phenomenon was not observed for diastolic BP for which the risk of stroke and CVD mortality was doubled at high levels (ie, ≥85 mmHg) in both communities.

The present study has several limitations. The number of men examined at baseline in the Tanushimaru and Ushibuka cohorts was relatively low. Also, we analysed baseline BP data only because repeated BP measurements during follow up were only available for part of the cohort. If more BP measurements had been taken into account during follow up, this would have increased the precision and probably yielded stronger associations with stroke and CVD mortality. We examined only men and findings might not apply to women. The study also has major strengths, including the large difference in fish consumption between the 2 communities within 1 culture with the same genetic background. Furthermore, no one was lost to follow up.

Dietary surveys were carried out in Tanushimaru in 1964 and in Ushibuka in 1971. The results of these surveys and the chemical analysis of food composites representing the average food consumption pattern of these men have been published previously. The average fish consumption was more than twice as high in the Ushibuka cohort (207 g/day) than in the Tanushimaru cohort (93 g/day). The average intake of the n-3 fatty acids EPA and DHA was 1.9 g/day in Ushibuka and 1.2 g/day in Tanushimaru. Saturated fat intake was low in both communities; 14 and 10 g/day, respectively. The average intake of other macronutrients, flavonoids and total energy showed little difference.

An overview of dietary intakes and CVD risk factors in both communities, including changes during follow up, is provided as a Web...
The main finding of the present study is that fishermen from Ushibuka, who were probably the largest fish consumers in that community, showed no relationship between systolic BP and long-term risk of mortality from stroke and total CVD. This is in contrast with the well-known graded relationship of systolic BP with the endpoints, as confirmed in the farming community of Tanushimaru, where farmers with a systolic BP >140 mmHg were at a 4-fold risk of dying from stroke and CVD compared to men with levels <120 mmHg.

An intriguing question is how to explain this difference in terms of the association of systolic BP with stroke and CVD mortality between Japanese farmers and fishermen. In 1994, Yamada et al examined Japanese middle-aged farmers from the village, Haze, and fishermen from the village, Kamishima. The average fish consumption was 100 g/day in the farming village and almost twice as high in the fishing village. In that study, the Intima Media Thickness and the number of plaques were much lower in the fishermen compared with the farmers. The most likely explanation for the differences in these measures of atherosclerosis is the difference in fish consumption between farmers and fishermen. A comparative study of Japanese and American whites aged 40–49 years showed that Japanese men had twice the level of marine-derived fatty acids in their blood and the lowest level of atherosclerosis. Significant differences between Japanese and American whites in Intima Media Thickness and Coronary Artery Calcification prevalence became non-significant after adjustment for n-3 fatty acids. This suggests that n-3 fatty acids might reduce the burden of atherosclerosis. The effect of very-long chain n-3 fatty acids (1.4 g/day) on plaque stability was examined in elderly patients waiting to undergo carotid endarterectomy. This study showed that n-3 fatty acids were rapidly incorporated into the plaque where they contributed to plaque stability. The authors concluded that the increased plaque stability might reduce the risk of cardiovascular events.

Remarkably, we found no difference in the association of diastolic BP with mortality from stroke and CVD between the Tanushimaru and Ushibuka cohorts. We have no explanation why only the association with systolic BP was blunted in Ushibuka men. However, in line with our hypothesis, one may speculate that n-3 fatty acids prevent rupture of atherosclerotic plaques, especially at peak BP levels. In summary, the present study showed that the established graded relationship of systolic BP with stroke and CVD mortality was not present in the fishing community of Ushibuka. These results suggest that the detrimental effect of systolic hypertension on CVD mortality could possibly be attenuated by very-long chain n-3 fatty acids. In the Honolulu Heart Program that started in 1965, CHD mortality rates were not related to the number of daily cigarettes smoked by 45–65 year-old Japanese-American men with a high fish intake (≥2 times/week). These data confirm the idea that a high fish intake could blunt the adverse effects of classical risk factors on CVD. This hypothesis, however, needs to be confirmed in other long-term, population-based studies with subjects who have a wide range of fish intake.

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Disclosure
Authors’ conflicts of interest: None.

References

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Conflict of interest: None.

**Supplemental Files**

**Supplemental File 1**

**Table S1.** Dietary Intakes of Middle-Aged Men in Tanushimaru in 1964 and Ushibuka in 1971 (Data Derived From References i–iv)

**Table S2.** Trends in Risk Factors in Farmers’ and Fishermen’s Villages in Japan

Please find supplemental file(s); http://dx.doi.org/10.1253/circj.CJ-10-0971