Almost one half of the Japanese men drank alcohol every day, while only a small percentage of the American men drank alcohol every day (46% versus 16%; $P < 0.01$). All the Japanese men ate fish twice a week or more, while only 17% of the American men did.

### Prevalence of subclinical atherosclerosis detected by EBT in men in the US and Japan

Prevalence of coronary artery calcium score >0, or ≥10 was strikingly lower among the Japanese men than the American men. Prevalence of coronary calcium score >0 was 47% among the American men, which is very similar to other reports in men in this age group in the US, while it was only 13% among the Japanese men. Similarly, prevalence of coronary calcium score ≥10 was 26% among the American men, and it was only 5% among the Japanese men. Among the American men, four subjects had coronary calcium score ≥100, while only one subject did among the Japanese men (Figure 1).

### Comparison of major independent risk factors and other factors by the presence of coronary calcium in each population

Table 2 shows the comparison of factors by the presence of coronary calcium (coronary calcium score >0 versus coronary calcium score = 0) in the American men as well as in the Japanese men. The American men with coronary calcium score >0 had significantly higher levels of fasting glucose, BMI, and waist circumference than those with coronary calcium score = 0. Levels of total cholesterol, HDL-C, or LDL-C did not

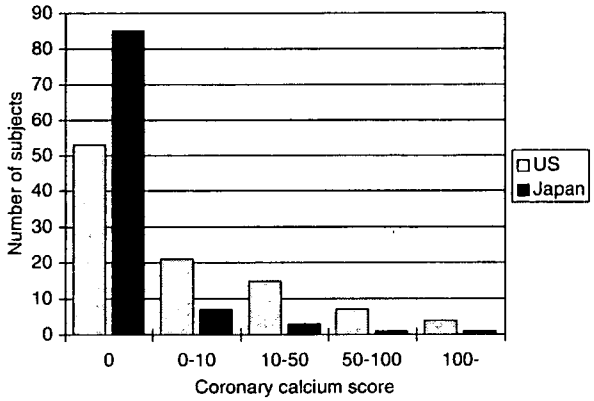


**Figure 1** Distribution of coronary calcium score (Agatston score) in the American men and Japanese men

**Table 2** Comparison of major independent risk factors and other factors between men who showed coronary calcium positive and negative in each of the American and Japanese men

| | US | | | Japan | | |
|---|---|---|---|---|---|---|
| Coronary calcium score | >0 (n = 47) Mean ± SD | 0 (n = 53) Mean ± SD | *P* | >0 (n = 13) Mean ± SD | 0 (n = 85) Mean ± SD | *P* |
| Age (year) | 45.1 ± 2.9 | 44.2 ± 2.8 | 0.09 | 45.2 ± 2.4 | 44.7 ± 2.9 | 0.42 |
| Systolic blood pressure (mmHg) | 115.6 ± 10.3 | 112.0 ± 8.7 | 0.07 | 125.9 ± 18.8 | 122.1 ± 13.3 | 0.30 |
| Diastolic blood pressure (mmHg) | 79.3 ± 5.7 | 77.6 ± 5.9 | 0.14 | 81.6 ± 11.9 | 78.2 ± 10.1 | 0.26 |
| Total cholesterol (mmol/l) | 4.98 ± 0.84 | 5.00 ± 0.80 | 0.90 | 6.01 ± 1.16 | 5.68 ± 0.94 | 0.13 |
| Triglycerides (mmol/l) | 1.34 (0.89, 2.08) | 1.29 (0.87, 1.77) | 0.42[b] | 1.75 (1.34, 2.82) | 1.45 (1.01, 1.98) | 0.20[b] |
| High density lipoprotein cholesterol (mmol/l) | 1.17 ± 0.27 | 1.21 ± 0.33 | 0.57 | 1.23 ± 0.26 | 1.44 ± 0.40 | 0.07 |
| Low density lipoprotein cholesterol (mmol/l) | 3.09 ± 0.83 | 3.11 ± 0.74 | 0.88 | 3.88 ± 1.13 | 3.47 ± 0.98 | 0.16 |
| Smoker (%) | 17.0 | 13.2 | 0.59[c] | 76.9 | 43.5 | 0.03[c] |
| Alcohol[a] (%) | 19.1 | 13.2 | 0.42[c] | 46.2 | 45.9 | 0.99[c] |
| Fasting blood glucose (mmol/l) | 5.43 ± 0.58 | 5.17 ± 0.39 | < 0.01 | 5.80 ± 0.45 | 5.73 ± 0.49 | 0.44 |
| Insulin (pmol/l) | 89.3 ± 44.3 | 84.2 ± 47.1 | 0.58 | 64.2 ± 23.7 | 55.9 ± 27.1 | 0.28 |
| Body mass index (kg/m$^2$) | 27.9 ± 3.7 | 26.3 ± 2.7 | 0.02 | 24.2 ± 4.1 | 23.1 ± 2.9 | 0.12 |
| Waist circumference (cm) | 98.7 ± 11.1 | 94.4 ± 8.1 | 0.03 | 87.4 ± 10.7 | 84.3 ± 8.1 | 0.14 |
| Height (cm) | 180.5 ± 6.7 | 180.7 ± 6.6 | 0.85 | 170.6 ± 4.5 | 170.2 ± 5.2 | 0.81 |
| C reactive protein (mg/l) | 1.04 (0.5–2.31) | 0.75 (0.44–2.02) | 0.53[b] | 1.02 (0.27–1.18) | 0.41 (0.21–0.73) | 0.09[b] |
| Fibrinogen (μmol/l) | 7.24 ± 2.18 | 6.96 ± 1.74 | 0.48 | 7.76 ± 2.07 | 6.82 ± 1.79 | 0.03 |

[a] Drink alcohol every day.
[b] Mann–Whitney test.
[c] Chi-square test.

appear to be different between the two groups in the American men. The Japanese men with coronary calcium score >0 had higher levels of total cholesterol, LDL-C, CRP, fibrinogen, lower levels of HDL-C, and higher prevalence of cigarette smoking than those with coronary calcium score = 0, although most of the differences did not reach statistical significance, due to the small number of subjects. We did the same analyses using the cut-point of calcium score 10 (coronary calcium score ≥10 versus <10). The results were very similar with those in Table 2, except the differences in the levels of both systolic and diastolic blood pressure reached statistical significance in both the Americans and the Japanese.

## Discussion

We observed strikingly lower prevalence of coronary artery calcium among the Japanese men than the American men despite a less favourable profile of several major independent risk factors: levels of systolic blood pressure, total cholesterol, and LDL-C, and the rate of cigarette smoking. The reason for this striking difference is largely unknown. Much higher levels of HDL-C among the Japanese in part account for the difference. Observed differences in obesity, especially central obesity, alcohol consumption, and fish intake may to some extent account for the difference in atherosclerosis formation.

Plausible mechanisms of the association of central obesity with atherosclerosis include small dense LDL, low HDL-C, large VLDL, high triglycerides, high systolic blood pressure, glucose intolerance, elevated CRP, abnormal coagulation/fibrinolytic profile, impaired endothelial function, and others.[9] Although levels of LDL-C were higher among the Japanese men, it is possible that the American men had a greater proportion of small dense LDL particles because they had much greater waist circumference and higher insulin levels.[10]

Higher levels of systolic blood pressure among the Japanese men and similar levels of triglycerides and fibrinogen in the two populations are inconsistent with the profile related to central obesity described above. The much higher alcohol consumption in the Japanese men may in part relate to higher levels of blood pressure.[11] Much higher intake of salt among the Japanese than Americans in general also may be in part responsible for the higher systolic blood pressure.[1,12] Similar levels of fibrinogen may be in part due to much higher prevalence of cigarette smoking among the Japanese men.

Much more frequent intake of alcohol among the Japanese than the Americans may in part relate to the lower prevalence of coronary calcium among the Japanese through the increase in HDL-C, reduction in blood clotting and platelet aggregation, increase in insulin sensitivity, and other mechanisms.[13]

The National Nutrition Survey in Japan showed that the Japanese eat more than 100 g of fish a day; men aged 40–49 eat fish about 120 g/day on average[1]. Average fish consumption in epidemiological studies examining its association with CHD in Western and some non-Western countries ranged from 14 g/day to 60 g/day.[14,15] This substantially higher fish consumption in the Japanese may exert some protective mechanisms against atherosclerosis, such as increasing the particle size of LDL,[16] or reducing the levels of CRP.[17]

Reported variation in cholesterol ester transfer protein polymorphisms may affect both HDL-C levels and atherosclerosis.[18] Variations in lipoprotein size, distribution, and particle concentration are related to atherosclerosis and CHD, independent of lipid levels.[18] These factors may be affected by genetic polymorphisms of enzymes such as lipoprotein lipase or hepatic lipase and may be influenced by certain environmental factors such as lack of exercise and diets leading to central obesity.[19]

Very high consumption of isoflavonoids from soy products in the Japanese in general may in part account for the difference,[1,20] although we did not examine soy consumption in this study.

Varying 'lag time' between exposure to risk factors and disease occurrence is unlikely to explain the difference because levels of total cholesterol in this post WWII birth cohort of US Caucasian men and Japanese men in Japan were very similar in the 1970s.[2] Prevalence of cigarette smoking in this birth cohort in Japan was already much higher than in the US in the 1980s.[1,12]

Various minimal numbers of pixels have been used in different studies for distinguishing true foci of calcium from noise, raging from one pixel to four adjacent pixels.[8,21–24] We employed a conservative threshold in this study: three adjacent pixels in our study. We also measured coronary calcium using a calcium volume score,[25] which has higher reproducibility between scans than coronary calcium score by Agatston methods. The correlation coefficient between a coronary calcium score and a calcium volume score was 0.997. Body size *per se* may possibly be related to increased prevalence of small lesions simply due to increased random scatter of the electron beam. If the prevalence of small lesions increases due to increased random scatter of the electron beam, there is a statistically significant positive correlation between a coronary calcium score and body mass index, especially when a coronary calcium score is <10. There was, however, no significant correlation between coronary calcium score and body mass index (correlation coefficient −0.26, $P = 0.895$).

Risk factor profiles of the examined population in Japan do not seem to be much different from those in the general population in Japan. The levels of total cholesterol and HDL-C as well as the rates of alcohol drinking and cigarette smoking in this population were very similar to the numbers reported from the National Nutrition Survey.[1]

There are several limitations of the study. First, the study was cross-sectional in design and we cannot establish a causal relationship. Second, the sample size of the study was too small to conduct robust multi-variable analyses. Third, the subjects in the Pittsburgh site were not randomly selected but volunteers. The results of the Pittsburgh site, therefore, cannot be generalized to the US population.

In this volunteer sample, however, the risk relationship should be similar with that in a randomly selected population, because it is highly unlikely that the participants of this study had previous knowledge of their own coronary calcium score. Based on the levels of total cholesterol and the prevalence of cigarette smoking, the participants could be somewhat healthier than a randomly selected population.[26] If this is the case, the prevalence of coronary calcium in a randomly selected population would be higher and the difference in the prevalence of coronary calcium would be much greater. One population-based study in the US reported that the prevalence of coronary artery calcium among men aged 40–49 was 42%.[21]

Two studies in the US reported the prevalence among men in this age group who were either physician- or self-referred, was around 45%.[22,23] It is, therefore, unlikely that the prevalence of coronary artery calcium in the study population is significantly different from that in a randomly selected population.

Much lower prevalence of coronary calcium, despite a less favourable profile of most major independent risk factors in the Japanese, might imply that there are strong protective factors against atherosclerosis in the Japanese. Further investigation by evaluating and comparing the extent and severity of subclinical atherosclerosis in these populations and its relation to various factors is of critical importance.

## Acknowledgements

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**KEY MESSAGES**

- National surveys showed that risk factor profiles for atherosclerosis around 1990 were similar in men in the post World War II birth cohorts in the US and Japan, except much higher prevalence of cigarette smoking in Japanese men and much higher prevalence of obesity in American men.
- Cross-sectional study examining 200 men aged 40–49 revealed that the prevalence of coronary calcium detected by electron-beam computed tomography was substantially lower in the Japanese than in the Americans (13% versus 47%), despite the fact that the Japanese had significantly higher levels of systolic blood pressure, total and low density lipoprotein cholesterol, as well as higher prevalence of cigarette smoking.
- The reason explaining this lower prevalence of coronary calcium in the Japanese men remains unknown. Further investigation is of critical importance.

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# Commentary: Use of EBCT in epidemiological studies: the effect of noise and body size on coronary calcium scores

Elizabeth F Hall

Electron beam computerized tomography (EBCT) is a non-invasive scanning technique that allows both detection and quantification of coronary artery calcium. Although only 20% of atherosclerotic plaque is calcified, the presence of coronary artery calcium in post-mortem specimens is a marker for the presence of atherosclerotic plaque and the quantity of calcium correlates with total atheroma burden.[1]

Available for over a decade, EBCT has been used extensively in the clinical assessment of patients at high risk of coronary heart disease, predominantly in the US.[2] Another promising application for EBCT is as a screening tool for coronary atheroma in epidemiological studies, particularly in young asymptomatic cohorts. Although fewer in number than those studies utilizing EBCT in clinical settings, there have been a number of recent reports of epidemiological studies using EBCT in participants with no evidence of pre-existing coronary heart disease.[3–6] Sekikawa *et al.* report on such a study in this issue, where they used EBCT to address the question of whether men born after the Second World War in America and Japan show differences in levels of atherosclerosis taking into account differences in cardiovascular risk.[7]

The validity of EBCT has been tested primarily in clinical patients who have high pre-test probability of disease.[2] The validity of the technique in populations with a low prevalence of disease has not been systematically studied, but there are indications that it is less robust in these groups.

Chest diameter and other measures of body size correlated with it are positively correlated with image noise on coronary EBCT scans.[8] Thus, unless adequately accounted for, noise can be mistaken for calcium on EBCT images leading to false positive scores, particularly in those with a high body mass index. The Agatston score,[9] the most widely used method for quantifying calcium on EBCT scans, which was utilized in Sekikawa's study, attempts to eliminate the effect of image noise by employing both a minimum density and a minimum area threshold when identifying calcium in coronary artery CT images. The density threshold of 130 Hounsfield Units has been used consistently in subsequent studies. There has however been considerable variation in the minimum area threshold employed in subsequent studies, from the 1 $mm^2$ in Agatston's original study to a sensitive 0.52 $mm^2$ and a more specific 2.05 $mm^2$.[4,5] This variation has usually been in response to concerns about false positive coronary calcium scores or poor inter-scan variability attributable to image noise when sensitive thresholds are used to define calcium in patients with low coronary calcium scores.

Many of the studies in younger cohorts have reported a positive association between body mass index and positive coronary calcium scores.[3–6] One reported that the association observed between body mass index and a positive coronary calcium score in a cohort aged 28–40 years diminished as the area threshold used

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CLINICAL RESEARCH STUDY

# Association between fish consumption and all-cause and cause-specific mortality in Japan: NIPPON DATA80, 1980-99

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**KEYWORDS:**
Fish;
Epidemiology;
Japanese;
All-cause mortality;
Coronary heart disease;
Cerebral infarction;
Cerebral hemorrhage

**PURPOSE:** Although high consumption of fish may be one of the contributing factors for Japanese longevity, no epidemiological study using Japanese data has tested this hypothesis.

**SUBJECTS AND METHODS:** The relationship between fish consumption and all-cause as well as cause-specific mortality was analyzed using the database of NIPPON DATA80. At baseline in 1980, history, physical, and blood biochemical measurement and a nutritional survey by the food-frequency method were performed in randomly selected community-based subjects aged 30 years and over in Japan. After exclusion of subjects with significant comorbidities at baseline, we followed 3 945 men and 4 934 women for 19 years. Men and women were analyzed comprehensively. Age- and sex-adjusted and multivariate adjusted relative risk for all-cause or cause-specific mortality was calculated using a Cox proportional hazards model with delayed entry.

**RESULTS:** During 19 years of followup, there were 1 745 deaths. Subjects were divided into 5 groups according to fish consumption frequency. The multivariate Cox analyses showed that relative risks for subjects who ate fish more than twice daily compared with those of subjects who ate 1 to 2 times weekly were 0.99 (95% confidence intervals: 0.77-1.27) for all-cause, 1.26 (0.70-2.29) for stroke, 0.92 (0.20-4.23) for cerebral hemorrhage, 1.09 (0.48-2.43) for cerebral infarction, and 0.91 (0.35-2.35) for coronary heart disease mortality.

**CONCLUSION:** Our results did not provide evidence in support of the fish hypothesis, perhaps because the majority of the Japanese subjects in the study ate fish more than the threshold level shown to be beneficial in the previous studies.



The current life expectancy of the Japanese is the longest in the world,[1] and their nutritional intake pattern is likely to contribute at least in part to their longevity. The fish intake of the Japanese is relatively high,[2,3] and ecological studies across several culturally different countries generated a hypothesis that high fish intake may be one of the factors for Japanese longevity.[3-6] Seven out of the 11 primary prospective cohort studies have found beneficial effects of fish intake on coronary heart disease events, coronary heart disease death, sudden cardiac death, or all-cause mortal-

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ity.[7-17] Furthermore, 2 interventional studies on postmyocardial infarction patients,[18,19] 3 case control studies,[20-22] and 3 subanalyses of the primary studies[23-25] also demonstrated protective effects of fish against coronary heart disease. However, no epidemiological study on the Japanese population living in Japan has examined the above hypothesis. Ideally, in order to probe the hypothesis, the association between fish consumption and health outcome within the Japanese population living in Japan must be demonstrated. Accordingly, we analyzed the relationship between fish consumption and all-cause and cause-specific mortality using the database of the National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged, 1980 (NIPPON DATA80), which includes more than 10 000 subjects in Japan who were followed for 19 years.[26-28]

## Methods

### Subjects

The subjects in this cohort were participants in the 1980 National Survey on Circulatory Disorders.[29] A total of 10 546 community-based subjects aged 30 years and over in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of history-taking, physical examinations, blood tests, and a self-administered questionnaire on lifestyle, including an essential nutritional survey by the food-frequency method. In the previous study, the cohort was followed until 1994 (NIPPON DATA80)[26-28], but for the present study, we extended the follow-up period until 1999 (NIPPON DATA80, 1980-99). The overall population aged 30 years and over in the 300 participating health districts numbered 13 771. Therefore, the participation rate of the survey was 76.6% (10 546 of 13 771) before exclusion for reasons mentioned below.

We reviewed the residence records of all the study subjects to check whether they were alive or dead. In case of deaths, the causes were examined. To clarify the cause of death, we used the National Vital Statistics. In accordance with Japan's Family Registration Law, all death certificates issued by physicians were forwarded to the Ministry of Health and Welfare via the public health centers in the district of residency. The underlying causes of death were coded according to the 9th International Classification of Disease for the National Vital Statistics until the end of 1994 and according to the 10th International Classification of Disease from the beginning of 1995. We confirmed death in each district by computer-matching of data from the Vital Statistics, using the district, sex, and dates of birth and death as key codes.

Of 10 546 subjects, a total of 1 667 were excluded for the following reasons: past history of coronary disease, stroke, cancer or significant comorbidities such as renal insufficiency: 539; some missing information at the baseline survey: 258; and lost to followup: 870. At the beginning of the study in 1980, we were allowed to record the present address of each subject, but not the permanent address. These 870 subjects included those who changed their addresses more than a certain number of times and we lost their present addresses. Without their present addresses, we could not link to their vital records. We analyzed the remaining 8 879 subjects (3 945 men and 4 934 women). There was no significant difference between subjects who were lost to followup and those who were censored with regard to, for instance, sex-specific mean total cholesterol (191 vs. 188 mg/dl for men, 194 vs. 192 mg/dl for women, respectively). Therefore, the potential bias regarding the 870 subjects lost to followup is thought to be negligible. Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science for Ethical Issues (No. 12–18, 2000).

### Biochemical and baseline examinations

The baseline surveys were conducted by public health centers. Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated subjects after at least 5 minutes of rest. Hypertension was defined as systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher, use of antihypertensive agents, or any combination of these criteria. Height in stocking feet and weight in light clothing were measured. The body mass index was calculated as weight (kg) divided by the square of height ($m^2$).

A lifestyle survey was carried out using a self-administered questionnaire, which asked about the usual average consumption of 31 food items. Fish consumption was queried using 5 categories: 2 times or more per day, about 1 time per day, about 1 time per 2 days, about 1 to 2 times per week, and less than once per week. Public health nurses rechecked information with subjects regarding fish and other food consumption, smoking, drinking habit, and present and past medical histories.

Non-fasting blood samples were drawn and centrifuged within 60 minutes of collection and then stored at −70°C until analysis. Total cholesterol was analyzed in a sequential autoanalyzer (SMA12/60; Technicon, Tarrytown, NY) at a single laboratory (Osaka Medical Center for Health Science and Promotion). This laboratory is a member of the Cholesterol Reference Method Laboratory Network (CRMLN),[30,31] and the precision and accuracy for the measurement of serum cholesterol were certified in the Lipid Standardization Program administered by the Centers for Disease Control and Prevention, Atlanta, GA. The serum concentration of glucose was measured by the cupric-neocuproline method.[32] Diabetes was defined as a serum glu-

**Table 1** Baseline characteristics according to fish consumption among 3 945 men and 4 934 women: -NIPPON DATA80: 1980-99----

| | 2+/day | 1/day | 1/2 days | 1-2/wk | Seldom | P ($\chi^2$ or ANOVA) |
|---|---|---|---|---|---|---|
| N | 569 | 2911 | 2865 | 2269 | 265 | |
| Male (%) | 56 | 47 | 43 | 39 | 45 | <0.0001 |
| Age (year) | 53.4 ± 12.0 | 50.8 ± 12.9 | 49.4 ± 13.1 | 50.3 ± 13.5 | 53.0 ± 13.8 | <0.0001 |
| Body mass index ($kg/m^2$) | 22.8 ± 3.2 | 22.8 ± 3.1 | 22.6 ± 3.1 | 22.7 ± 3.3 | 22.4 ± 2.9 | 0.13 |
| Total cholesterol (mg/dl) | 187 ± 36 | 189 ± 33 | 189 ± 33 | 188 ± 34 | 187 ± 35 | 0.45 |
| Hypertension (%) | 53 | 46 | 42 | 44 | 49 | <0.0001 |
| Diabetes (%) | 6.2 | 5.3 | 5.1 | 4.6 | 9.1 | 0.03 |
| Current smoker (%) | 36 | 35 | 31 | 32 | 36 | 0.002 |
| Alcohol drinker (%) | 51 | 47 | 44 | 40 | 42 | <0.0001 |

Data are shown in % or mean ± SD ANOVA = analysis of variance.

cose concentration of 200 mg/dl or greater and/or self-reporting of diabetes.

### Statistical analysis

SAS version 8.02 for Windows (SAS Institute, Cary, NC) was used throughout the study. Men and women were analyzed comprehensively. The chi-square test was used to compare dichotomous variables, and a one-way analysis of variance was used to compare means among the 5 groups according to fish consumption.

Age- and sex-adjusted and multivariate adjusted relative risk for all-cause or cause-specific mortality was calculated using a Cox's proportional hazard model with delayed entry (left truncation) (model 1). For multivariate analyses, age (left truncation), sex, cigarette smoking (current smoker or not) and alcohol intake (occasional and daily drinker or not), hypertension (dichotomous), body mass index (<27 $kg/m^2$ or >=27 $kg/m^2$), and diabetes (dichotomous) were entered as covariates (model 2). The third model (model 3) included all the model 2 covariates and serum total cholesterol concentration (linear). The 1 to 2 times per week fish consumption group was taken as the reference. To examine for sex differences, interaction terms of fish consumption and sex were used. There were no interactions between them on mortality. Tests of linear trends across groups were conducted by assigning an ordinal value from 1 to 5 for each level of consumption, and modeling this as a continuous variable in separate Cox proportional hazards models.

Linear hypotheses about the regression coefficients were tested for all the covariates mentioned above. All of them became linear by modeling them as described, except for the fish consumption continuous variable. All $P$ values were two-tailed, and $P < 0.05$ was considered significant. Data are presented as the mean ± standard deviation (SD) unless stated otherwise.

## Results

### Baseline characteristics

The baseline characteristics in each fish consumption category for men and women combined are shown in Table 1. Relatively few subjects (6% and 3% of the total subjects) were in the more than twice per day or less than once per week groups. Except for these two extreme categories, there were more than 2 200 subjects in each category. The mean age was higher and there were more subjects with hypertension and diabetes in these two extreme categories. Among the subjects who ate fish more than twice per day, there were more men, and thus alcohol drinkers were most frequent among the groups. Total cholesterol concentration and body mass index were not different among the 5 groups.

### Fish consumption and outcome: age- and sex-adjusted outcome and multivariate Cox analyses

Table 2 shows the total person-years, numbers of cases, mortality per 1 000 person-years, relative risks, and 95% confidence intervals by age and sex-adjusted (model 1), and multivariate-adjusted (models 2 and 3) deaths due to all causes, cerebral infarction, cerebral hemorrhage, and coronary heart disease for each category of fish consumption. All-cause and cause-specific mortality were not different among the groups no matter what kinds of model were used, and all the relative risks were near 1.0 with the all confidence intervals crossed 1.0, and the $P$ values for trend were more than 0.4. The model 3 multivariate Cox analyses showed that relative risks for subjects who ate fish more than twice daily compared with those of subjects who ate fish 1 to 2 times weekly were 0.99 (95% confidence intervals: 0.77-1.27) for all-cause, 1.26 (0.70-2.29) for stroke, 0.92 (0.20-4.23) for cerebral hemorrhage, 1.09 (0.48-2.43) for cerebral infarction, and 0.91 (0.35-2.35) for coronary heart disease mortality.

**Table 2** Relative risks of all cause and cause-specific mortality according to fish consumption among 8 879 men and women: NIPPON DATA80: 1980-99

| | 2+/day | 1/day | 1/2 days | 1-2/wk | Seldom | Trend P |
|---|---|---|---|---|---|---|
| Total person-years | 9738 | 50488 | 50066 | 39149 | 4433 | |
| All-cause death, N | 138 | 584 | 496 | 450 | 77 | (total = 1,745) |
| /1 000 person-years | 14.2 | 11.6 | 9.9 | 11.5 | 17.4 | |
| RR1 (95%CI) | 0.98 (0.76-1.26) | 1.01 (0.87-1.19) | 0.96 (0.84-1.10) | 1 | 1.10 (0.86-1.42) | 0.87 |
| RR2 (95%CI) | 1.00 (0.77-1.29) | 1.03 (0.88-1.20) | 0.98 (0.85-1.12) | 1 | 1.12 (0.87-1.44) | 0.98 |
| RR3 (95%CI) | 0.99 (0.77-1.27) | 1.03 (0.88-1.20) | 0.98 (0.85-1.12) | 1 | 1.12 (0.87-1.44) | 0.94 |
| Stroke death, N | 26 | 101 | 80 | 67 | 14 | (total = 288) |
| /1 000 person-years | 2.7 | 2 | 1.6 | 1.7 | 3.2 | |
| RR1 (95%CI) | 1.21 (0.67-2.19) | 1.17 (0.80-1.70) | 1.07 (0.76-1.50) | 1 | 1.37 (0.75-2.48) | 0.96 |
| RR2 (95%CI) | 1.28 (0.71-2.32) | 1.20 (0.82-1.75) | 1.10 (0.78-1.54) | 1 | 1.34 (0.74-2.44) | 0.50 |
| RR3 (95%CI) | 1.26 (0.70-2.29) | 1.20 (0.82-1.75) | 1.09 (0.78-1.53) | 1 | 1.34 (0.73-2.44) | 0.52 |
| Cerebral hemorrhage death, N | 5 | 19 | 26 | 12 | 1 | (total = 63) |
| /1 000 person-years | 0.5 | 0.4 | 0.5 | 0.3 | 0.2 | |
| RR1 (95%CI) | 0.94 (0.21-4.20) | 1.00 (0.39-2.57) | 1.73 (0.83-3.61) | 1 | 0.60 (0.08-4.73) | 0.98 |
| RR2 (95%CI) | 0.93 (0.20-4.28) | 0.99 (0.38-2.55) | 1.74 (0.84-3.64) | 1 | 0.56 (0.07-4.41) | 0.97 |
| RR3 (95%CI) | 0.92 (0.20-4.23) | 0.99 (0.38-2.56) | 1.77 (0.84-3.69) | 1 | 0.55 (0.07-4.37) | 0.98 |
| Cerebral infarction death, N | 15 | 60 | 40 | 43 | 7 | (total = 165) |
| /1 000 person-years | 1.5 | 1.2 | 0.8 | 1.1 | 1.6 | |
| RR1 (95%CI) | 1.06 (0.48-2.34) | 1.08 (0.67-1.79) | 0.85 (0.54-1.34) | 1 | 1.00 (0.43-2.30) | 0.97 |
| RR2 (95%CI) | 1.11 (0.50-2.47) | 1.11 (0.67-1.85) | 0.87 (0.55-1.37) | 1 | 1.01 (0.44-2.33) | 0.70 |
| RR3 (95%CI) | 1.09 (0.48-2.43) | 1.11 (0.67-1.84) | 0.86 (0.54-1.36) | 1 | 1.00 (0.43-3.23) | 0.72 |
| Coronary heart disease death, N | 9 | 37 | 39 | 32 | 7 | (total = 142) |
| /1 000 person-years | 0.9 | 0.7 | 0.8 | 0.8 | 1.6 | |
| RR1 (95%CI) | 0.80 (0.31-2.06) | 0.86 (0.48-1.54) | 1.06 (0.65-1.74) | 1 | 1.48 (0.63-3.43) | 0.42 |
| RR2 (95%CI) | 0.86 (0.33-2.23) | 0.90 (0.50-1.61) | 1.10 (0.67-1.80) | 1 | 1.45 (0.62-3.37) | 0.51 |
| RR3 (95%CI) | 0.91 (0.35-2.35) | 0.91 (0.51-1.62) | 1.07 (0.66-1.76) | 1 | 1.47 (0.63-3.39) | 0.54 |

Total person-years of follow-up, death case number (N), mortality per 1 000 person-years (/1,000 person-years), relative risks (RR) and 95% confidence intervals (95% CI) are shown. RR1 (model 1): age and sex adjusted. RR2 (model 2): adjusted by age, sex, smoking, alcohol drinking, hypertension, body mass index and diabetes. RR3 (model 3): adjusted by model 2 covariates and total cholesterol.

Thus, there appeared to be little association between fish consumption and all-cause mortality in the Japanese population of the present study. Some of the results for cause-specific mortality appear to support a protective effect; however, uncertainty is so large that no strong conclusion can be made.

## Discussion

Although the majority of the prospective cohort studies have found an inverse association between fish consumption and risk of coronary heart disease or all-cause mortality[7,10,12-15,17,18] (Table 3), the 4 cohort studies did not find such associations[8,9,11,16] (Table 3). One of these was the study on the Japanese American population living in Hawaii, and the authors speculated that almost everyone in the study population ate some fish regularly and their consumption level might have been higher than that which provided the maximal effect.[9] "How much fish consumption is necessary to elicit a cardiovascular protective effect?" is the central question. A U.S. Physicians Health Study by Albert and coworkers found a threshold of fish consumption at 1 serving per week for preventing sudden cardiac death.[13] The study by Mozaffarian and coworkers found that more than 2 servings of fish per week were associated with lower risk for coronary heart disease.[17] Two recent meta-analyses suggested that further reduction in coronary heart disease mortality might be attained by consuming fish more than once per week; however, definitive conclusions were not made because of lack of significant trend *P* values.[33,34] Taking the above evidence together, the recent U.S. Dietary Guidelines 2005 recommends 2 servings of fish per week to decrease risk of heart disease,[35] and the United Kingdom Scientific Advisory Committee on Nutrition recommends at least two portions of fish a week to reduce the risk of death from heart disease.[36] The results of the present study agree with the above recommendations and other reports that demonstrated the benefit of 1 to 2 servings of fish weekly and no further benefits at higher intake.

The majority of the epidemiological studies took the less than 1 fish consumption per month group as the reference for statistical analysis.[7,9,11-13,15-17] Fish consumption in Japan has been reported to be around 100 g per day on the average, whereas in North America it has been reported to be a quarter of that.[2,3,37] In the present study, only a few subjects consumed fish less than once per week. Therefore, it is understandable that significant beneficial effects of fish consumption were not demonstrated in the present study, perhaps because the majority of the Japanese subjects in the study ate fish more than the threshold level shown to be beneficial in the previous studies.

**Table 3** Summary of epidemiological and interventional studies investigating fish consumption and CHD morbidity, mortality or all-cause mortality

| Study type | Author | Yr of pub | Population | No. of subjects | Exposure comparison category (fish intake etc) | Outcome measures | RR (95% CI) etc |
|---|---|---|---|---|---|---|---|
| Cohort | Kromhout[7] | 1985 | Dutch | 852 men for 20 yrs, 78 CHD deaths | 0 g/day vs 30–44 g/day | CHD death | 0.36 (0.14–0.93) |
| Cohort | Vollset[8] | 1985 | Norwegian | 11 000 men for 13 yrs, 2587 deaths | 0–4 times/mo vs >= 25/mo | all-cause, CHD death | NS for trend |
| Cohort | Curb[9] | 1985 | Japanese Hawaiian | 7615 men for 12 yrs | almost never vs almost daily, and 0 g/day vs >168 g/day | CHD death | NS for trend |
| Cohort | Norell[10] | 1986 | Swedish | 10 966 men & women, twins for 15 years; 1195 deaths | no & low vs high intake | MI death | 0.70 (0.50–0.98) |
| Cohort | Ascherio[11] | 1995 | US, Health Professionals Follow-up Study | 44 895 men for 6 yrs; 1543 coronary events | < 1/mo vs >=6/wk | CHD event | 1.14 (0.86–1.51) |
| Cohort | Daviglus[12] | 1997 | US, Chicago Western Electric Study | 1882 men for 30 yrs (47 153 PY); 430 CHD deaths | 0 g/day vs >=35 g/day | CHD death | 0.62 (0.40–0.94) |
| Cohort | Albert[13] | 1998 | US, Physicians' Health Study | 20 551 men for 11 yrs; 133 SCD | <1/mo vs >=1/wk | SCD | 0.48 (0.24–0.96) |
| Cohort | Yuan[14] | 2001 | Chinese in Shanghai | 18 244 men for 12 yrs | >=200 g/wk vs < 50 g/wk | MI, all-cause death | MI: 0.41 (0.22–0.78) all-cause: 0.7 (0.69–0.91) |
| Cohort | Hu[15] | 2002 | US, the Nurses' Health Study | 84 688 women for 16 yrs | < 1/mo vs >=5/wk | fatal and nonfatal CHD | 0.69 (0.52–0.93 |
| Cohort | Osler[16] | 2003 | Danish | 4 513 men and 3 984 women for 5–18 yrs | < 1/mo vs 1/wk | all-cause and CHD death, CHD event | NS |
| Cohort | Mozaffarian[17] | 2003 | US | 3 910 men & women for 9.3 yrs | < 1/mo vs >=1/mo | CHD death, CHD arrhythmic death and nonfatal CHD | Trend P = 0.002 |
| Intervention | Burr[18] | 1989 | UK, 2nd. MI Prevention (DART) | 2003 post-MI men | no advice vs fish advice | all-cause death | 0.71 (0.54–0.93) |
| Intervention | GISSI group[19] | 1999 | Italian, GISSI 2nd. MI Prevention | 11 324 men & women post-MI for 3.5 yrs | 1/2 received supplementary n-3 PUFA | nonfatal MI, stroke, death | 0.85 (0.74–0.98) |
| Case-control | Gramenzi[20] | 1990 | Italian women, post-MI & controls | 287 women post-MI & 649 hospital controls | low 1/3 vs high 1/3 | MI | 0.6 (P < 0.05) |
| Case-control | Siscovick[21] | 1995 | US | 334 primary cardiac arrest & 493 controls | 0 vs 4.1–7.4 g n-3/mo | primary cardiac arrest | 0.50 (0.4–0.8) |
| Case-control | Guallar[22] | 2002 | Israeli & Europeans | 684 men post-MI & 724 controls | adipose-tissue DHA levels in quintiles; Q1 vs Q5 | MI | 0.59 (0.30–1.19) (trend P = 0.02) |
| Subanalyse | | | | | | | |
| Cohort | Rodriguez[23] | 1996 | Japanese Hawaiian | 8006 men for 23 yrs | in > 30/day cigarette smoker, fish < 2/wk vs >=2/wk | CHD death | 0.50 (0.28–0.91) |
| Nested case-control | Albert[24] | 2002 | US, Physicians' Health Study | 94 sudden cardiac death case in 17 yrs vs 184 controls | n-3 quartile 1 vs 4 | SCD | 0.10 (0.02–0.48) |
| Cohort | Hu[25] | 2003 | US, the Nurses' Health Study | 5103 type 2 diabetic women for 16 yrs | < 1/mo vs >=5/wk | fatal, nonfatal CHD, all-cause death | CHD: 0.36 (0.20–0.66), death: 0.48 (0.29–0.80) |

Abbreviations: pub = publication, RR = relative risk, CI = confidence intervals, vs = versus, CHD = coronary heart disease, NS = statistically not significant, MI = myocardial infarction, SCD = sudden cardiac death, PUFA = poly-unsaturated fatty acids, DHA = docosahexaenoic acid, wk = week, mo = month, yr = year.

The proposed potential mechanisms by which fish consumption or omega-3 fatty acids may reduce risk for cardiovascular disease are related to reducing susceptibility to ventricular arrhythmia and to an antithrombogenic effect, hypotriglyceridemic effect, antiatherosclerotic effect, promotion of nitric oxide–induced endothelial relaxation, and a mildly hypotensive effect.[38] Although clinical studies have demonstrated an increase in bleeding time and/or a decrease in platelet aggregability with fish oil administration,[39-52] epidemiological stud-

ies have denied the risk of increasing cerebral hemorrhage associated with fish consumption.[41-45]

## Limitations of the study

As stated earlier, there was no low/negligible fish intake group for appropriate comparison purposes in the present study. That is a limitation of this study.

We used mortality data as end points, which may have led to the misclassification of the cause of deaths. However, it has been reported that the death certificate diagnosis for stroke and cancer in Japan is quite accurate.[46,47] Because computed tomography scanners were becoming commonplace at the beginning of the 1980s, 84-88% of stroke patients had computed tomography scanning in that decade[47] and that percentage rose to over 90% by the first half of the 1990s[49] even in rural areas of Japan; therefore, the diagnoses of stroke in the National Vital Statistics were considered to be reliable. The ratio of cerebral infarction to cerebral hemorrhage in the present study was 2.6 to 1, which is similar to that of epidemiologic studies during the past 20 years in Japan.[48-50] However, it has also been reported that most cases of sudden cardiac death are described on Japanese death certificates as "coronary heart disease," "heart failure," or "unknown cause."[51] Lack of reliable sudden death data in the present study is the other limitation, because some of the previous studies on fish consumption and outcome reported that fish consumption was associated with a reduction in sudden cardiac death.[13,24] Furthermore, mortality statistics for coronary heart disease may have been underestimated by the end of 1994 using ICD9, because deaths coded "heart failure" might hide some coronary events.[51-53]

It was unfortunate that we did not measure fatty acid biomarker to validate the food frequency questionnaire used in the present study for fish consumption.

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# Incidence of Acute Myocardial Infarction in Takashima, Shiga, Japan

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**Background** The incidence and mortality from ischemic heart disease (IHD) in Japan seem to be among the lowest of all the industrialized countries, but there are few reliable registers of acute myocardial infarction (AMI).

**Methods and Results** To assess the incidence of AMI in Takashima County, Shiga, Japan, from 1988 to 1998 and compare the data with similar registers in the world, cases of AMI or sudden death presumed from myocardial ischemia were registered. The criteria of AMI were based on the WHO MONICA Projects. The medical records of all the hospitals inside as well as outside the county, the original death records in the health center, and the ambulance records in the county were investigated and 291 cases were registered (190 males, 101 females; average age (mean±SD), 69.5±12.2). The 28-day and 24-h case fatality was 38.1% and 33.0%, respectively. Age-adjusted annual incidence of AMI per 100,000 population aged between 25 and 74 years were 58.2 for men and 18.0 for women. The incidence of AMI showed a constant trend from 1988 to 1998.

**Conclusion** The results confirmed that Japan has the lowest incidence of AMI among the industrialized countries. (*Circ J* 2005; **69:** 404–408)

**Key Words:** Epidemiology; Japan; Myocardial infarction; Population

The incidence and mortality from ischemic heart disease (IHD) in Japan seem to be among the lowest of all the industrialized countries and the age-adjusted IHD mortality in Japan has been decreasing gradually since approximately 1970[1–4] However, there are few reliable community-based studies of acute myocardial infarction (AMI) in Japan[5–9] and most of them included only a small number of annual events and had short research periods. The low mortality rates for IHD in Japan may be partly artifact, because the majority of deaths in the category of diseases of the heart are attributed to "heart failure" whereas this category is rarely used in other industrialized countries[10] Although the possibility that the mortality from IHD in the post World War II birth cohort in Japan might have actually increased has been suggested[10] another study reported no increase at all[11] Therefore, it is difficult to determine whether the incidence and mortality from AMI are increasing or decreasing in Japan.

Ongoing AMI registration was established in Takashima County in Shiga Prefecture, Japan, in 1988 in order to measure trends in the incidence and case-fatality of AMI. At the same time, we have been registering stroke since 1988[12] so that we can clarify the incidence ratio of stroke and AMI, and compare the incidence of AMI in Japan with other Western countries.

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## Methods

*Geographic Conditions of the Research Area*

Shiga prefecture is located in the approximate geographic center of Japan, bordering the Kyoto municipal area to the south-west. Lake Biwa, the largest lake in Japan, is located in the east of Takashima County and the Hira-san Gangs runs north–south to the west. Takashima County has a stable population of approximately 53,000 with 17.6% of the population (about 10,000) aged 65 years or older. It is a farming community, although only approximately 7% of the residents are engaged in primary industries; almost 38% of the residents are involved in secondary industries and 55% in tertiary industries. The majority of residents in the latter 2 categories work outside the county.

There are 2 community hospitals in Takashima County; the one in the south is a public facility providing 261 beds, and the other in the north is a private facility providing 72 beds. Although percutaneous catheter interventional therapy for AMI[13,14] had begun at public hospital in 1998, prior to this year almost all cases of AMI were transferred to tertiary hospitals (4 facilities) outside the county. However, almost all the patients in the county were taken to one of the 2 local hospitals by ambulance before transfer, so the Takashima hospitals had the medical records of the patients who were subsequently be registered as having AMI.

**Table 1 Fatal Cases of AMI in Takashima, Shiga, Japan, 1988–1998**

| | |
|---|---|
| *Total fatal cases within 28 days* | *111* |
| *Sudden cardiac death within 24 h* | *96* |
| *Out-of-hospital sudden death* | *74* |
| *Death within 24 h or during transfer* | *22* |
| *Death from 24 h to 28 days* | *15* |
| *28-day case fatality* | *38.1% (111/291)* |
| *28-day case fatality for hospitalized cases* | *17.1% (37/217)* |
| *28-day case fatality for hospitalized 24-h survivors* | *7.6% (15/195)* |
| *Pre-hospital case fatality* | *25.4% (74/291)* |
| *24-h case fatality* | *33.0% (96/291)* |
| *Pre-hospital death/all fatal cases* | *66.7% (74/111)* |
| *Death within 24 h/all fatal cases* | *86.5% (96/111)* |

*AMI, acute myocardial infarction.*

**Table 2 Incidence of Case of Survival and Death After AMI by 10-Year Age Groups in Takashima, Shiga, Japan, 1988–1998**

| *Age group (years)* | *Total cases (M/F)* | *Non-fatal cases* | *Fatal cases after admission* | *Fatal cases before admission* |
|---|---|---|---|---|
| *20–29* | *2 (2/0)* | *2 (100.0%)* | *0 (0%)* | *0 (0%)* |
| *30–39* | *3 (2/1)* | *2 (66.7%)* | *0 (0%)* | *1 (33.3%)* |
| *40–49* | *13 (13/0)* | *11 (84.6%)* | *1 (7.7%)* | *1 (7.7%)* |
| *50–59* | *35 (29/6)* | *23 (65.7%)* | *4 (11.4%)* | *8 (22.9%)* |
| *60–69* | *95 (66/29)* | *66 (69.5%)* | *5 (5.3%)* | *24 (25.3%)* |
| *70–79* | *79 (49/30)* | *49 (62.3%)* | *10 (12.7%)* | *20 (25.3%)* |
| *80–89* | *54 (26/28)* | *24 (44.4%)* | *15 (27.8%)* | *15 (27.8%)* |
| *≥90* | *10 (3/7)* | *3 (30.0%)* | *2 (20.0%)* | *5 (50.0%)* |
| *Total* | *291 (190/101)* | *180 (61.9%)* | *37 (12.7%)* | *74 (25.4%)* |

*AMI, acute myocardial infarction.*

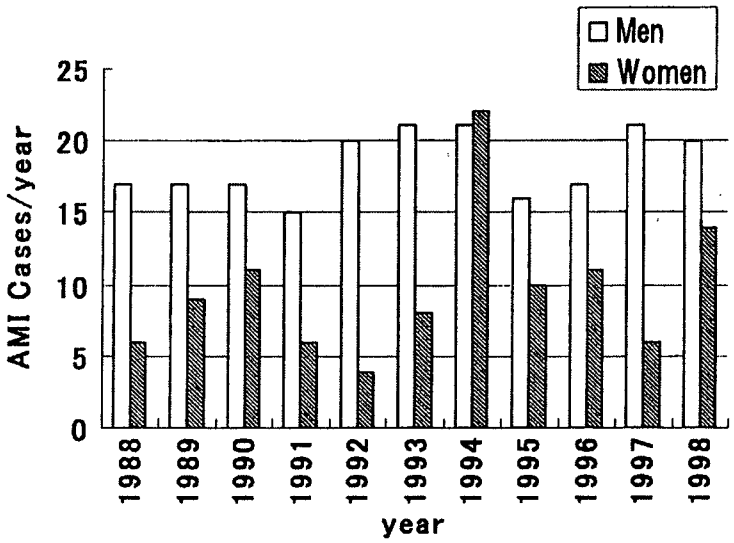


Fig 1. Annual incidence of AMI from 1988 to 1998 in Takashima, Shiga, Japan. There is a constant trend from 1988 to 1998, except for 1994, but the difference is not statistically significant by chi-square test.

*Registration*

Registered patients included all those who were residents of Takashima County and had either experienced an AMI died out-of-hospital from sudden cardiac death suspected to be related to myocardial ischemia. The criteria of AMI were based on the WHO MONICA Projects (Monitoring of Trends and Determinants in Cardiovascular Disease)[15] We registered all cases that met the inclusion criteria on the basis of the medical records from all the relevant hospitals inside and outside the county. We investigated the original death records at the county health center and the county ambulance records with the permission of the Ministry of Public Management, Home Affaires, Post and Telecommunications, Japan. Patients' privacy was protected.

We used the registration form of the Monitoring System for Cardiovascular Disease commissioned by the Ministry of Health and Welfare[16] Items recorded at registration of an AMI were the date and time of onset, age, sex, location at the time of onset, time of admission, electrocardiographic findings, region of infarction, Q wave or non-Q-wave myocardial infarction (MI), peak creatine kinase, coronary risk factors, history of MI, pre-infarction angina, complications in the acute stage, Killip's classification, fatality within 28 days, cause of death, angiographic findings, acute therapy,

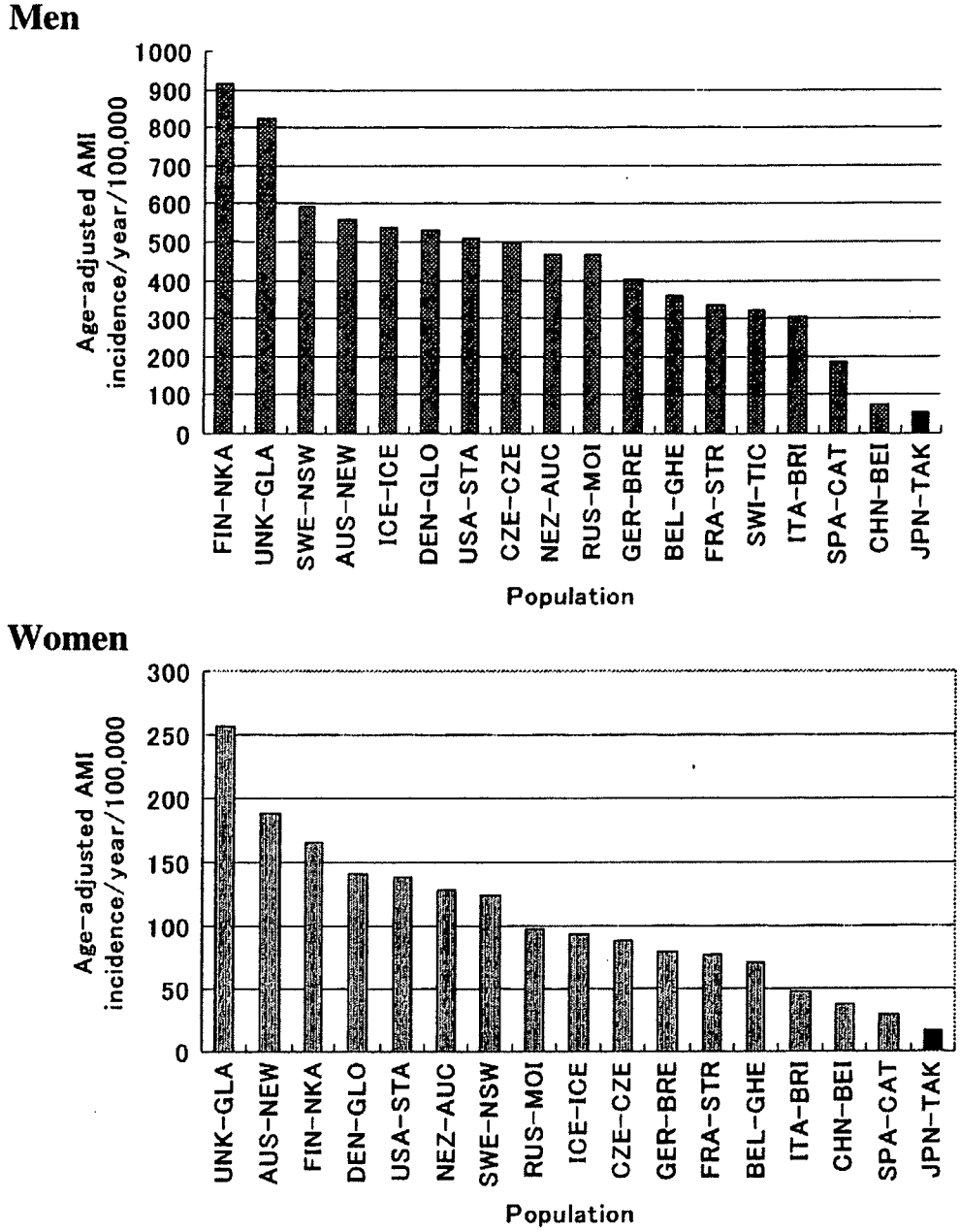


Fig 2. Age-adjusted annual incidence rate of first AMI per 100,000 population for men (Top) and women (Bottom) aged between 35 and 64 years compared with WHO MONICA Project (WHO MONICA data 1985–1987). The incidence rates of AMI in Takashima County in 1988–1998 were the lowest in the world for both men and women. FIN-NKA, Finland-North Karelia; UNK-GLA, United Kingdom-Glasgow; ICE-ICE, Iceland-Iceland; AUS-NEW = Australia-Newcastle; SWE-NSW, Sweden-Northern Sweden; DEN-GLO, Denmark-Glostrup; NEZ-AUC, New Zealand-Auckland; USA-STA, United States of America-Stanford; CZE-CZE, Czech Republic-Czech Republic; BEL-GHE, Belgium-Ghent; GER-BRE, Germany-Bremen; FRA-STR, France-Strasbourg; RUS-MOI, Russia-Moscow Intervention; ITA-BRI, Italy-Area Brianza; SWI-TIC, Switzerland-Ticino; SPA-CAT, Spain-Catalonia; CHN-BEI, China-Beijing; JPN-TAK, Japan-Takashima.

and New York Heart Association functional classification[17] at discharge.

Definite sudden cardiac death was defined as fatal cases with gross evidence of fresh myocardial infarction and/or recent coronary occlusion at necropsy. Possible sudden cardiac death was defined as fatal cases in which there was no other strong evidence of another cause of death, clinically or at autopsy, with typical, atypical or inadequately described symptoms; or without typical, atypical or inadequately described symptoms but with evidence of chronic coronary occlusion or stenosis or old myocardial scarring at necropsy; or a history of chronic IHD such as definite or possible MI, coronary insufficiency or angina pectoris in the absence of significant valvular disease or cardiomyopathy.

In cases of silent MI diagnosed later, the onset dates

were taken as the oldest possible date of documentation.

*Data Analysis*

We calculated age-specific rates in 10-year age groups and age-specific incidence rates were determined by the population of the relevant age group in Takashima County at the 1993 census[18] We calculated 2 types of age-adjusted incidence rates, using the Japanese population aged 20 years and older, and those aged between 35 and 64 years from the 1980 census as the standard population to allow comparison with the results of the WHO MONICA Project[19] Direct age standardization of the incidence rates was done according to the WHO MONICA Project, using the truncated Segi world standard population weights 6, 6, 6, 5, 4 and 4 for the 5-year age groups of 35–39 to 60–64 years, respectively[20]

## Results

We registered 291 cases (males: 190 cases; females: 101 cases; averaged age (mean±SD): 69.5±12.2, max: 96 years; min: 29 years) during 11 years between the beginning of 1988 and the end of 1998, which included sudden cardiac death cases caused by definite or possible myocardial ischemia. Table 1 shows the fatal cases. The total number of fatal cases within 28 days was 111 (approximately 2.4 % of the total mortality of all the ages during the 11 years), which included 74 cases of out-of-hospital sudden cardiac death or cardiopulmonary arrest, 22 cases of sudden cardiac death within 24 h of arriving at hospital or during transfer to tertiary hospital, and 15 cases of death from 24 h to 28 days; in total there were 96 cases of sudden cardiac death within 24 h and 37 cases of death after admission and within 28 days. The 28-day case fatality, 28-day case fatality for hospitalized cases and 28-day case fatality for hospitalized 24-h survivors was 38.1% (111/291), 17.1% (37/217) and 7.6% (15/195), respectively. Prehospital case fatality and 24-h case fatality was 25.4% (74/291) and 33.0% (96/291), respectively. The rate of prehospital death for all fatal cases were 66.7% (74/111) and the rate of death within 24 h for all fatal cases was 86.5% (96/111).

Table 2 shows the incidence of survival and fatal cases by 10-year age groups. The peak incidence by 10-year age groups was in the 60–69 year olds. The ratio of males to females was very high in the age groups under 59 years, but the percentage of females became higher with advancing age and the ratio was less than one in the groups over 80 years old. There was a tendency for the total case fatality to became higher with advancing age. The incidence of AMI showed a constant trend from 1988 to 1998 except for the year 1994 (Fig 1).

Table 3 shows the age-specific and age-adjusted annual incidence rate of first AMI per 100,000 population aged 20 years and older. The age-specific incidence rates for the total and for men and women, respectively, increased with advancing age.

Age-adjusted incidence rates for those aged between 35 and 64 years were 55.5/year per 100,000 population for men and 9.1/year per 100,000 population for women. The comparison of the age-adjusted annual incidence rates for men and women aged from 35 to 64 years with the WHO MONICA Project[15] is shown in Fig 2.

**Table 3 Age-Specific and Age-Adjusted Annual Incidence Rates of First AMI per 100,000 Population Aged 20 Years and Older in Takashima, Shiga, Japan, 1988–1998**

| *Age group (years)* | *Total* | *Male* | *Female* |
|---|---|---|---|
| *20–29* | *3.0* | *6.0* | *0* |
| *30–39* | *4.3* | *5.7* | *2.8* |
| *40–49* | *13.8* | *24.2* | *0* |
| *50–59* | *47.5* | *80.0* | *16.4* |
| *60–69* | *109.9* | *155.9* | *66.8* |
| *70–79* | *152.8* | *239.5* | *96.9* |
| *≥80* | *258.0* | *346.8* | *210.8* |
| *Crude rate* | *61.5* | *83.5* | *41.1* |
| *Age-adjusted ratea* | *42.3* | *65.2* | *23.0* |

*Adjusted to 1980 Japanese population aged 20 years and older.*

## Discussion

We found that the incidence of AMI in Takashima county, Japan showed a constant trend from 1988 to 1998 except for 1994, and our results confirmed that Japan has the lowest incidence of AMI among the industrialized countries. A comprehensive registration system for diseases such as AMI is sine qua non in determining the incidence in a particular area. A system to capture all patients in the study area, together with accurate diagnosis, is required to ensure comprehensive registration. Factors that reduce the comprehensiveness of a register are missing cases of sudden death for which there is not a confirmed diagnosis, missing AMI patients admitted to hospitals outside the registration area, and non-registration because of the AMI patient being cared for at home or in a nursing home.

We registered cases of out-of-hospital sudden cardiac death, but because electrocardiogram findings and the concentrations of cardiac enzymes are often not available in such cases, we had to base registration on the patients' location and symptoms at onset and their history of coronary heart disease. We tried to register only cases with definite and possible causes of sudden coronary death according to the MONICA registry's definition. The rate of pre-hospital death for all fatal cases was 66.7% in this study. In the WHO MONICA Project, the average rates for men and women were 70% and 64%, respectively[21] Therefore, we believe that cases of other causes of death were excluded from registration as cases of sudden cardiac death in this study.

To ensure that eligible patients hospitalized outside the county were not excluded, registration was also conducted at the main tertiary hospitals. For example, 23 cases were not transferred to either of the local hospitals in the acute phase, but 12 had county ambulance records and we obtained information of the other 11 cases from the hospitals outside the county: of these, 8 in-hospital deaths were located in the original death records in the county health center (5 occurred outside the prefecture, 3 within the prefecture) and the remaining 3 cases were hospitalized outside the county without using the county ambulance system. The major limitation of our data collection related to cases of non-fatal AMI managed outside the 4 main medical facilities; however, we estimated that there would be very few patients who would go to hospitals that were not participating in our registration system.

Almost 100% of the residents of Japan have public health insurance offered by sources such as the Ministry of Health and Welfare. Health insurance is not expensive and

the policies cover all diseases, excluding injury from road traffic accident. Therefore, the usual practice in Japan is that patients in the county would consult a general physician, who if AMI was suspected from the symptoms and signs would almost always refer the patient to a secondary or tertiary hospitals for extensive investigation. Therefore we believe that only a few cases of non-fatal AMI were not registered.

We have conducted a previous registration of AMI cases in 7 areas in Japan, including Takashima County, based mainly on hospital records. The age-adjusted first AMI incidence rates per 100,000 for all ages in Akita, Ehime, Nagano, Takashima, Hokkaido, Osaka and Okinawa areas were 15.0, 19.5, 22.6, 22.6, 24.7, 24.9, and 26.0 respectively[22] Therefore, the incidence rates in Takashima in the median of the 7 regions. In the present study, we extended the comprehensiveness of the register by investigating the original death records at the county health center and the ambulance records; as a result, the first AMI incidence rate increased from 22.6 per 100,000 population of all ages to 30.5.

Although we have registered cases of AMI and stroke in this area since 1988, the incidence of AMI showed a constant trend from 1988 to 1998 except for the year 1994 (Fig 1). Some Japanese studies have reported that the incidence of AMI did not vary much during the research period[5,7] and although many cardiologists and physicians are under the impression that the incidence of AMI in Japan is increasing, the crude incidence has not changed greatly in a decade. Before 1993, many physicians in Japan used the term "acute heart failure" for sudden death of unknown etiology for the diagnosis on the medical certificate, but in 1994 the Ministry of Health and Welfare recommended that it not be used; however, some physicians might have used the term "AMI", even though they were not certain of the definite diagnosis and this may be a reason for the higher incidence of AMI in women in 1994 than in the other years. As the incidence of AMI in men did not change in 1994, it is likely that the increased incidence in women in 1994 was a random fluctuation.

The age-adjusted annual incidence rates for men and women aged from 35 to 64 years were compared with those of the WHO MONICA Project[15] (Fig 2). Takashima County has the lowest incidence in the world for AMI in men, women and both sexes. Our results confirmed that Japan has the lowest incidence of AMI among the industrialized countries as reported by other investigators. Ongoing monitoring of AMI in Takashima County is feasible and will promote understanding of the reasons for the continuing decline in AMI incidence that has been noted in all regions of Japan.

*Acknowledgments*

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Original Article

# Birthweight and risk factors for cardiovascular diseases in Japanese schoolchildren

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**Abstract**

***Background***: Low birthweight (LBW) is associated with an increased risk for atherosclerotic coronary heart disease (ACHD) later in life. However, little information is currently available on the relationship between birthweight (BW) and risk factors for ACHD in children.

***Methods***: The relationship between BW and risk factors for ACHD was evaluated in 330 Japanese children (187 boys and 143 girls) aged between 7 and 12 years, who underwent screening for lifestyle-related diseases in Okinawa, Japan. Routine chemical methods were used to determine the serum concentrations of lipids, apolipoproteins, uric acid and glucose. Serum insulin and adiponectin were measured by sandwich enzyme-linked immunosorbent assay.

***Results***: BW was significantly correlated with serum concentrations of adiponectin ($r = 0.163$, $P = 0.003$) and uric acid ($r = -0.166$, $P = 0.003$), but not with insulin, lipids or apolipoproteins. These correlations were still significant even after adjusting for age, gender and body mass index (BMI) percentile (BW and adiponectin, $r = 0.239$, $P = 0.000$; BW and uric acid, $r = -0.247$, $P = 0.000$). In addition, BW was correlated with high-density lipoprotein-cholesterol (HDL-C) only after adjusting for age, gender and BMI percentile ($r = 0.117$, $P = 0.034$). In a stepwise multiple regression analysis, BW was a significant predictive variable for adiponectin and uric acid. However, weight velocity (weight gain/year) was a stronger predictive variable than BW for both adiponectin and uric acid. BW was not a significant predictive variable for HDL-C. Adiponectin was the strongest predictive variable for HDL-C.

***Conclusion***: BW is related to serum concentrations of adiponectin and uric acid. However, weight velocity was a stronger determinant of serum adiponectin and uric acid levels than BW in Japanese schoolchildren. Thus, it may be important to control weight gain to prevent the development of ACHD in children, especially in children with LBW.

**Key words** adiponectin, atherosclerosis, birthweight, BMI, insulin resistance, weight velocity.

Several epidemiological studies have indicated that low birthweight (LBW) is associated with an increased prevalence of, and mortality due to, atherosclerotic coronary heart disease (ACHD) later in life.[1–3] Fetal nutrition and early postnatal growth are thought to contribute to this association.[1,4] The initial stage of atherosclerosis begins in childhood and progresses from fatty streaks to raised lesions in adolescence and young adulthood.[5,6] This process is accelerated in children with risk factors for ACHD.[7] Thus, it seems reasonable to consider the relationship between birthweight (BW) and risk factors for ACHD in children. To date, most studies have been performed in adults and have indicated that there are significant relationships between BW and risk factors for ACHD including blood pressure, cholesterol, and insulin sensitivity.[8–10] However, conventional risk factors for ACHD acquired later in life such as smoking, obesity, diabetes mellitus and so on may affect these relationships. In contrast, children rarely drink alcohol or smoke, and usually exercise regularly at school. Thus, environmental factors that affect the relationship between BW and risk factors may have less of an effect in children than in adults. Several reports are now available in children. However, the relations between BW and risk factors for ACHD are still controversial.[11–21] While some studies have reported a significant relationship, others have reported no association between BW and risk factors for ACHD.

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In the present study we investigated the relationships between BW and conventional risk factors for ACHD in Japanese schoolchildren. In addition, we studied the relationships between BW and adiponectin and uric acid. Adiponectin is a so-called adipocytokine that is secreted from adipocytes. In recent reports, adiponectin levels have been shown to be lower in the presence of prevalent coronary artery diseases.[22,23] Higher adiponectin levels were associated with a lower risk of myocardial infarction in the Health Professionals Follow-up Study.[24] This relationship can be only partly explained by differences in blood lipids and is independent of inflammation and glycemic status.[24] In the case of uric acid, many reports have demonstrated that uric acid is not an independent risk factor for ACHD.[25,26] However, recent studies have shown that serum uric acid levels are positively associated with hypertension, inflammation and ACHD mediated by endothelial dysfunction and pathologic vascular remodeling.[27] The aim of the present study was to clarify the effect of BW on conventional and newly identified risk factors for ACHD in Japanese schoolchildren.

## Methods

### *Subjects*

Informed consent was obtained from the parents of all of the children. The present study was approved by the Review Board of the University of the Ryukyus. We studied 330 Japanese children (187 boys and 143 girls) aged between 7 and 12 years, who underwent screening for lifestyle-related diseases in Okinawa, Japan. Body mass index (BMI) was calculated as weight [kg]/height$^2$ [m$^2$]. BMI percentiles were obtained based on data regarding BMI percentiles for Japanese children.[28] The mother provided BW based on the *Maternal and Child Health Handbook*. None of the children studied was receiving therapy for weight reduction or drugs to affect lipid metabolism. Venous blood was drawn after an overnight fast.

### *Laboratory measurements*

Routine chemical methods were used to determine the serum concentrations of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), uric acid, glucose, and electrolytes. Serum insulin was measured by two-step sandwich enzyme-linked immunosorbent assay (ELISA; SRL, Hachioji, Japan). Low-density lipoprotein-cholesterol (LDL-C) was calculated as TC – HDL-C – TG/5. Apolipoproteins (A-I and B) were measured by the turbidity immunoassay method.[29] The serum adiponectin concentration was measured by sandwich ELISA (Otsuka Pharmaceutical, Tokusima, Japan). LDL-size was evaluated by electrophoresis in non-denaturing polyacrylamide gradient gels on precast Multigel-LP (2–15%; Daiichi Pure Chemical, Tokyo, Japan), as described previously.[30] Insulin resistance and insulin sensitivity were calculated using the homeostasis model approximation index (HOMA2-IR) and the quantitative insulin-sensitivity check index (QUICKI).[31,32] These equations, both based on fasting glucose and insulin, correlate well with insulin dynamics as measured on the hyperinsulinemic clamp and the i.v. glucose tolerance test. Weight velocity (WV) between birth and current age was calculated as kg gained per year.

### *Statistical evaluation*

Differences in parameters among subjects in three groups (BW: small, middle, large) were determined using the Kruskal–Wallis test. Parameters in these three groups were compared with Scheffe's multiple comparison test. Age and gender were adjusted for by an analysis of covariance (ancova). Pearson and partial correlation coefficients were computed to assess the associations between BW and other parameters. A stepwise multiple regression analysis was performed by entering the independent variable with the highest partial correlation coefficient at each step, until no variable remained with $F > 4$. Group differences or correlations with $P < 0.05$ were considered to be statistically significant. All statistical analysis was performed using Stat View J-5.0 software (SAS Institute, Cary, NC, USA).

## Results

The BW in the present children ranged from 1520 to 4704 g, and 8.4% of the BW were <2500 g. To understand the relation between BW and lipids and other parameters, subjects were divided into three groups based on BW percentiles (small, <10th; middle, 10th–90th; large, >90th). As shown in Table 1, no difference was found in BMI percentiles, lipids, apolipoproteins, insulin resistance (HOMA2-IR) or insulin sensitivity (QUICKI). Significant graded relationships between these three groups were found in adiponectin and uric acid. However, significant differences in adiponectin were found only between small and middle BW groups. In the case of uric acid, significant differences were found between the small and large and between the middle and large BW groups.

As shown in Table 2, BW was correlated with adiponectin ($r = 0.163$, $P = 0.003$) and inversely correlated with uric acid ($r = -0.166$, $P = 0.003$). Significant correlations were not found in other parameters listed in Table 2. After being corrected for age, gender and BMI percentile, significant correlations were still found in both adiponectin and uric acid (adiponectin, $r = 0.239$, $P = 0.000$; uric acid, $r = -0.247$,

**Table 1** Clinical and chemical data on children adjusted for age and gender (mean ± SEM)

| | Small | | Middle | | Large |
|---|---|---|---|---|---|
| | <10th Percentile | *P* | 10th–90th Percentile | *P* | >90th Percentile |
| *n* | 33 | | 264 | | 33 |
| Birthweight (kg) | 2.21 ± 0.05 | <0.0001 | 3.16 ± 0.02 | <0.0001 | 3.94 ± 0.04*** |
| BMI percentile | 67.4 ± 6.2 | n.s. | 63.8 ± 2.0 | n.s. | 74.8 ± 4.3 |
| Weight velocity (kg/year) | 3.85 ± 0.23 | n.s. | 3.54 ± 0.07 | n.s. | 3.81 ± 0.20 |
| Adiponectin (μg/mL) | 8.0 ± 0.5 | n.s. | 9.2 ± 0.2 | n.s. | 10.4 ± 0.7* |
| Glucose (mg/dL)† | 91 ± 1 | n.s. | 91 ± 1 | n.s. | 92 ± 1 |
| Insulin (μU/mL) | 10.0 ± 0.4 | n.s. | 9.2 ± 0.5 | n.s. | 9.9 ± 1.7 |
| HOMA2-IR | 1.3 ± 0.2 | n.s. | 1.2 ± 0.1 | n.s. | 1.3 ± 0.2 |
| QUICKI | 0.37 ± 0.01 | n.s. | 0.38 ± 0.01 | n.s. | 0.37 ± 0.01 |
| TC (mg/dL)‡ | 175 ± 5 | n.s. | 176 ± 2 | n.s. | 183 ± 5 |
| TG (mg/dL)§ | 82 ± 7 | n.s. | 74 ± 3 | n.s. | 79 ± 9 |
| LDL-C (mg/dL)‡ | 103 ± 4 | n.s. | 102 ± 2 | n.s. | 104 ± 4 |
| HDL-C (mg/dL)‡ | 58 ± 2 | n.s. | 62 ± 1 | n.s. | 64 ± 2 |
| ApoA-I (mg/dL) | 132 ± 3 | n.s. | 141 ± 4 | n.s. | 140 ± 3 |
| ApoB (mg/dL) | 76 ± 3 | n.s. | 73 ± 1 | n.s. | 75 ± 3 |
| Uric acid (mg/dL) | 5.2 ± 0.2 | <0.01 | 4.6 ± 0.1 | n.s. | 4.4 ± 0.1** |
| LDL-size (nm) | 26.9 ± 0.2 | n.s. | 27.2 ± 0.1 | n.s. | 27.2 ± 0.2 |

Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; HOMA2-IR, homeostasis model approximation index; LDL-C, low-density lipoprotein-cholesterol; QUICKI, quantitative insulin-sensitivity check index; TC, total cholesterol; TG, triglyceride. †To convert to mmol/L, divide by 18; ‡to convert to mmol/L, multiply by 0.0259; §to convert to mmol/L, multiply by 0.0113. *$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$; significantly different from small.

$P = 0.000$). In addition, HDL-C was correlated with BW only after being corrected for age, gender and BMI percentile. Serum concentrations of adiponectin, uric acid and HDL-C are associated with many risk factors for ACHD. Thus, to understand the contribution of BW to serum concentrations of adiponectin, uric acid and HDL-C in schoolchildren, we performed a stepwise multiple regression analysis with adiponectin, uric acid and HDL-C as dependent variables and the other parameters as independent variables. As shown in Table 3, BW was a significant predictive variable for adiponectin and uric acid but not for HDL-C. However, WV (weight gain/year) was a stronger predictive variable than BW for both adiponectin and uric acid. HDL-C was also a stronger predictive variable than BW for adiponectin. Adiponectin was the strongest predictive variable for HDL-C. Table 4 shows the correlations between WV and several parameters. WV was positively correlated with age, gender, BMI percentile and uric acid, and inversely associated with adiponectin. After being corrected for age, gender and BMI percentile, the correlations of WV with adiponectin and uric acid were still significant (partial correlation in Table 4).

**Table 2** Birthweight and variables

| | Simple correlation | | Partial correlation | |
|---|---|---|---|---|
| | *r*† | *P* | *r*‡ | *P* |
| Age | 0.034 | 0.539 | | |
| Gender | −0.070 | 0.207 | | |
| BMI percentile | 0.084 | 0.128 | | |
| Weight velocity | 0.028 | 0.614 | −0.077 | 0.163 |
| Adiponectin | 0.163 | 0.003 | 0.239 | 0.000 |
| Glucose | 0.057 | 0.308 | 0.057 | 0.303 |
| Log insulin | 0.020 | 0.722 | −0.093 | 0.092 |
| Log HOMA2-IR | 0.020 | 0.712 | −0.083 | 0.133 |
| QUICKI | −0.023 | 0.672 | 0.081 | 0.143 |
| TC | 0.013 | 0.814 | 0.003 | 0.957 |
| Log TG | −0.074 | 0.181 | -0.098 | 0.076 |
| LDL-C | −0.009 | 0.876 | −0.029 | 0.600 |
| HDL-C | 0.073 | 0.189 | 0.117 | 0.034 |
| ApoA-I | 0.038 | 0.498 | 0.050 | 0.366 |
| ApoB | −0.035 | 0.529 | −0.061 | 0.270 |
| Uric acid | −0.166 | 0.003 | −0.247 | 0.000 |
| LDL-size | 0.022 | 0.693 | 0.068 | 0.219 |

Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; HOMA2-IR, homeostasis model approximation index; LDL-C, low-density lipoprotein-cholesterol; QUICKI, quantitative insulin-sensitivity check index; TC, total cholesterol; TG, triglyceride. †Pearson correlation coefficient; ‡variables corrected for age, gender and BMI percentile.

## Discussion

In the present study, serum concentrations of adiponectin, uric acid and HDL-C, but not insulin, lipids (except HDL-C) or apolipoproteins were correlated with BW. A significant correlation was not recognized between BW and BMI percentile.

**Table 3** Stepwise multiple regression analysis of correlates of adiponectin, uric acid and HDL-C

| | Independent parameters | $r$ | $r^2$ |
|---|---|---|---|
| Adiponectin | | | |
| Step 1 | WV | 0.511 | 0.261 |
| Step 2 | WV, HDL-C | 0.568 | 0.323 |
| Step 3 | WV, HDL-C, BW | 0.590 | 0.348 |
| Step 4 | WV, HDL-C, BW, ApoB | 0.605 | 0.368 |
| Step 5 | WV, HDL-C, BW, ApoB, BMI percentile | 0.614 | 0.378 |
| Steps 1–5: $P < 0.0001$ | | | |
| Uric acid | | | |
| Step 1 | WV | 0.537 | 0.288 |
| Step 2 | WV, BW | 0.566 | 0.321 |
| Step 3 | WV, BW, ApoB | 0.592 | 0.350 |
| Step 4 | WV, BW, ApoB, LDL-C | 0.619 | 0.384 |
| Steps 1–4: $P < 0.0001$ | | | |
| HDL-C | | | |
| Step 1 | Adiponectin | 0.415 | 0.172 |
| Step 2 | Adiponectin, log TG | 0.502 | 0.252 |
| Step 3 | Adiponectin, log TG, TC | 0.605 | 0.366 |
| Steps 1–3: $P < 0.0001$ | | | |

Apo, apolipoprotein; BMI, body mass index; BW, birthweight; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride; WV, weight velocity.

**Table 4** Weight velocity and variables

| | Simple correlation | | Partial correlation | |
|---|---|---|---|---|
| | $r^\dagger$ | $P$ | $r^\ddagger$ | $P$ |
| Age | 0.236 | 0.000 | | |
| Gender | 0.161 | 0.004 | | |
| BMI percentile | 0.835 | 0.000 | | |
| Adiponectin | −0.512 | 0.000 | −0.188 | 0.001 |
| Uric acid | 0.542 | 0.000 | 0.243 | 0.000 |

†Pearson correlation coefficient; ‡variables corrected for age, gender and BMI percentile.

BMI, body mass index.

### *Birthweight and adiponectin*

Clinically, serum concentrations of adiponectin are decreased in subjects with obesity, type 2 diabetes or coronary heart disease.[22,33] Similar to the results in adults, serum concentrations of adiponectin in obese children are inversely correlated with body fat and, as a result, serum adiponectin levels are significantly lower than those in non-obese children.[34,35] In the present study we confirmed these findings in Japanese schoolchildren (T. Ohta, unpubl. data, 2005: BMI percentile >95th, 6.6 ± 0.3 μg/mL; <95th, 10.2 ± 0.2 μg/mL). Regarding the relationship between adiponectin and BW, Cianfarani *et al.* reported that serum adiponectin concentrations were reduced in children who were born small for gestational age (SGA).[36] In contrast, Lopez-Bermejo *et al.* reported opposite results: serum adiponectin concentrations were higher in SGA children.[37] In the present study most of the children studied were not SGA. BW was positively correlated with serum concentrations of adiponectin. Thus, the present data extend the finding of Cianfarani *et al.* to non-SGA children. Although BW was an independent predictor for adiponectin, it had a much weaker contribution than WV in schoolchildren. This suggests that postnatal weight gain may affect the function of adipocytes more than fetal growth *in utero*.

### *Birthweight and uric acid*

Low birthweight correlates with impaired renal development and a reduced number of nephrons at birth.[38–40] Based on an animal study, a reduction in the number of nephrons results in an increase in proximal reabsorption.[41] Uric acid reabsorption is linked to proximal sodium reabsorption.[42] These serial findings might explain the inverse relationship between BW and uric acid. Most recently, Feig *et al.* reported that the serum uric acid level correlates inversely with BW in adolescents with essential hypertension.[41] In the present study we measured blood pressure in only 140 children (data not shown) and hypertensive children were not identified. Feig *et al.* did not provide any data on subjects with normal blood pressure. Because the present children were younger than the children in the Feig *et al.* study, the present data may suggest that children with LBW might have a risk for future development of hypertension. However, in the present study the most powerful predictor of the serum uric acid level was WV. As with adiponectin, postnatal weight gain seems to be more important than fetal growth *in utero* in the control of uric acid levels. To date, many studies have demonstrated that uric acid is not an independent risk factor for ACHD.[25,26] Conventional risk factors for ACHD such as LDL-C and apolipoprotein B influence serum uric acid levels (Table 3). Thus, further studies are needed to clarify the effect of uric acid on the future development of ACHD.

### *Birthweight and lipids and apolipoproteins*

Based on reports in adults, BW shows only a weak or no association with lipids and apolipoproteins.[9,21] Similar to the results in adults, weak inverse relationships between BW and lipids (TC and LDL-C) have been reported in 8-year-old Indian children.[11] Mean values of BW, TC and LDL-C in Indian children were lower than those in the present children (BW, 2.7–2.8 vs 3.14–3.15 kg; TC, 131 vs 172–183 mg/dL; LDL-C, 77 vs 96–110 mg/dL). Mortaz *et al.* reported that BW is not related to TC, TG, LDL-C, HDL-C, apolipoprotein A-I or apolipoprotein B in children (BW, <1850 g) aged 8–12 years.[12] The age distribution and lipid values of the present subjects were similar to the Mortaz *et al.* subjects and, as in their