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Original Article

## Association of Dietary Fat and Carbohydrate Consumption and Predicted Ten-year Risk for Developing Coronary Heart Disease in a General Japanese Population

Akira Minoura<sup>a</sup>, Da-Hong Wang<sup>a\*</sup>, Yoshie Sato<sup>b</sup>, Yu Zou<sup>a</sup>,  
Noriko Sakano<sup>c</sup>, Masayuki Kubo<sup>a</sup>, Kei Takemoto<sup>a</sup>, Chie Masatomi<sup>a</sup>, and Keiki Ogino<sup>a</sup>

Departments of <sup>a</sup>Public Health, and <sup>c</sup>Gerontology Research, Okayama University Graduate School of Medicine,  
Dentistry and Pharmaceutical Sciences, <sup>b</sup>Graduate School of Health Sciences, Okayama University, Okayama 700-8558, Japan

We examined the relationships between dietary carbohydrate, protein, fat, and the ratio of n6/n3 fatty acid intakes with the predicted 10-year coronary heart disease (CHD) risk in a general Japanese population. We used the Framingham risk score to determine the 10-year CHD risk of the subjects, who were employees of 6 companies in a single prefecture in Japan. After excluding the subjects who reported any history of angina pectoris, myocardial infarction, diabetes, or cancer, and those with missing data resulting in the inability of estimation of 10-year CHD risk and food intakes, the final data analysis was carried out for 809 subjects. The logistic regression models revealed a significantly increased odds ratio of 10-year CHD risk in the subjects with the highest tertile of carbohydrate intake (% energy) (odds ratio 3.64, 95% CI, 2.07–6.40); after adjustment for other variables, the odds ratio for the 10-year CHD risk was also higher in the subjects with the highest tertile of carbohydrate intake (odds ratio 1.72, 95% CI, 0.70–4.25). We also found that fat intake and the ratio of n6/n3 fatty acids were inversely associated with the predicted 10-year CHD risk ( $p$  for trend < 0.01). The present findings added evidence of a positive association of dietary carbohydrate and inverse associations of total fat and n6/n3 fatty acid ratio with the predicted 10-year CHD risk in a general Japanese population.

**Key words:** fat intake, carbohydrate intake, ratio of n6/n3 fatty acids, 10-year coronary heart disease risk, Japanese

In many developed countries, heart disease is one of the leading causes of death among adults [1–4]. In Japan, heart disease is now the second-ranked cause of death [4]. Unhealthy lifestyles, especially dietary habits, are believed to play a critical role in the development of heart disease [5–8]. The consumption of dietary fat, in particular saturated

fatty acids (SFAs), has long been blamed as one of the factors contributing to the development of coronary heart disease (CHD) [9–11], and a low-fat, high-carbohydrate diet is recommended for prevention against heart disease [12, 13]. However, in 1997, Katan *et al.* [14] raised a doubt about the benefit of a low-fat, high-carbohydrate diet in reducing cardiovascular disease. A large 8-year intervention trial with a diet low in total fat did not show any beneficial effect of this dietary pattern on the risk of CHD [15]. There are conflicting findings with regard to replacing

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\*Corresponding author. Phone: +81-86-235-7182; Fax: +81-86-226-0715  
E-mail: dahong@md.okayama-u.ac.jp (Wang. DH)

a high-fat diet with a high-carbohydrate diet in preventing coronary events and the mortality of heart disease [7, 16–19].

Framingham risk scoring has been widely used to predict the 10-year risk of developing CHD [20–22]. In the present study we used the Framingham risk score to determine the 10-year CHD risk of a general Japanese population, and we examined the relationships between the subjects' dietary macronutrient intakes and their predicted 10-year CHD risk.

## Subjects and Methods

**Subjects.** The study population was 847 individuals (360 men, 487 women) employed at 6 companies in Okayama Prefecture, Japan who participated in a worksite lifestyle intervention study from September to December of 2007. After excluding the subjects who reported any history of angina pectoris, myocardial infarction, diabetes, or cancer, or who had missing data resulting in the inability of estimation of their 10-year CHD risk and food intakes, the final data analysis was carried out for 809 subjects. The study was approved by the Ethics Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Written informed consent was obtained from all subjects.

**Measurements.** Body composition was evaluated using the following parameters: body weight, waist circumference, and body mass index (BMI), which was calculated by the body weight (kg)/height (m)<sup>2</sup>. Each subject had his or her blood pressure measured by a physician with the subject in a sitting position after resting for at least a few minutes.

Venous blood and urine samples were collected after an overnight fast of at least 10 h. Serum and plasma were used to measure the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamylpeptidase ( $\gamma$ -GTP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), high-sensitivity C-reactive protein (CRP), fasting glucose, insulin, and hemoglobin A1c (HbA1c). The homeostasis model assessment (HOMA-R) levels were calculated as the fasting insulin ( $\mu$ U/mL)  $\times$  fasting glucose (mg/dL)/405 [23].

**Estimation of 10-year CHD risk.** For each subject, we calculated the 10-year CHD risk score

based on Framingham risk scoring [20–21]. The risk factors included age, gender, TC and HDL-c concentrations, systolic blood pressure (SBP), and current smoking status [21]. The TC values were categorized as <160, 160–199, 200–239, 240–279, and  $\geq$  280 mg/dL; the HDL-c were categorized as  $\geq$  60, 50–59, 40–49, and < 40 mg/dL. The SBP values were categorized as <120, 120–129, 130–139, 140–159, and  $\geq$  160 mmHg. The 10-year CHD risk (%) was estimated by counting the subject's total point scores, and then we categorized < 10% as the low-risk group and  $\geq$  10% as the high-risk group.

**Lifestyle information.** The subjects' lifestyle data including diet, cigarette smoking, alcohol consumption, and exercise were obtained using self-reported questionnaires. The smoking status was classified into 2 groups: nonsmokers and current smokers. The frequency of alcohol consumption was classified into 3 groups: never, 3 times per week or below, and 4 times or above per week. The exercise habit was classified as no exercise, 5 times per week or below, and 6 times or above per week.

Habitual food consumption was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) according to food groups [24]. The subjects were asked to specify, for the previous 1–2 months, how often, on average, they consumed the foods in each food group in a week, either as indicated by the unit and portion size or by scoring the consumption status on a 4-point Likert scale consisting of the responses "not at all," "somewhat" (half of the general amount), "a general amount" (the amount consumed by people of the same gender and age), and "very much" (1.5 times the general amount). We used the residual method to adjust the nutrient intake information according to the total energy intake by performing a regression analysis [25].

**Data analysis.** Data comparisons between the < 10% and  $\geq$  10% 10-year CHD risk groups were performed by the Mann-Whitney *U*-test for the continuous variables and by the  $\chi^2$  test for the categorical variables. A Spearman correlation analysis was used to examine the association of 10-year CHD risk with the lifestyle and biochemistry variables. A binomial logistic regression analysis was used to evaluate the independent relationship of dietary nutrients with the 10-year CHD risk. All statistical analyses were carried out using SPSS (Statistical Package for the

Social Sciences) 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

The subjects' characteristics are shown in Table 1. The mean age of the subjects in the low CHD risk group (< 10% CHD risk, n = 721) was 41 years, and that of the subjects in the high CHD risk group ( $\geq$  10% CHD risk; n = 88) was 51 years. Among the  $\geq$  10% CHD risk group, most of the subjects (97.7%) were men. The values of BMI, waist circumference,

blood pressure, AST, ALT,  $\gamma$ -GTP, TC, TG, LDL-c, CRP, fasting glucose, and HbA1c were all significantly higher in the  $\geq$  10% CHD risk group compared to those of the < 10% CHD risk group, and the HDL-c levels were higher in the < 10% CHD risk group. There were more persons who frequently consumed alcohol in the  $\geq$  10% CHD risk group.

The values of daily carbohydrate intake (% energy) were higher and those of fat intake (% energy) and the ratio of n6/n3 fatty acids were lower in the  $\geq$  10% CHD risk group compared to those of the < 10% CHD risk group (Table 2).

**Table 1** Subject characteristics and clinical profiles by 10-year CHD risk

Variable	10-year CHD risk, median (min, max)		p <sup>b</sup>
	< 10% risk (n = 721)	$\geq$ 10% risk (n = 88)	
Age (year)	41 (18, 67)	51 (35, 67)	<0.001
Sex <sup>a</sup>			<0.001
Male	251 (34.8)	86 (97.7)	
Female	470 (65.2)	2 (2.3)	
BMI (kg/m <sup>2</sup> )	22.1 (14.5, 39.7)	23.9 (16.1, 37.17)	<0.001
Waist circumference (cm)	78.2 (53, 120)	85 (61.5, 113)	<0.001
Systolic blood pressure (mmHg)	125 (76, 221)	137 (83, 198)	<0.001
Diastolic blood pressure (mmHg)	75 (47, 152)	84 (45, 127)	<0.001
AST (IU/l)	19 (9, 78)	21 (9, 64)	<0.001
ALT (IU/l)	16 (4, 183)	23 (8, 93)	<0.001
$\gamma$ -GTP (IU/l)	18 (5, 933)	35 (13, 432)	<0.001
LDL-c (mg/dl)	121 (35, 331)	139 (64, 250)	<0.001
HDL-c (mg/dl)	64 (35, 119)	54 (31, 133)	<0.001
TG (mg/dl)	74 (18, 906)	128 (48, 600)	<0.001
Hs-CRP (mg/dl)	0.3 (0, 46.5)	0.4 (0.1, 5.9)	0.001
Fasting glucose (mg/dl)	90 (71, 148)	95.5 (68, 169)	<0.001
HbA1c (%)	4.9 (3.7, 7.8)	5 (4.4, 7.4)	0.001
Insulin ( $\mu$ U/ml)	4.4 (0.5, 54.4)	4.5 (1.5, 22.4)	0.818
HOMA-R	0.9 (0.1, 16.1)	1 (0.3, 6.6)	0.467
Smoking <sup>a</sup>			0.081
Nonsmoker	489 (67.8)	50 (56.8)	
Past smoker	56 (7.8)	7 (8)	
Current smoker	176 (24.4)	31 (35.2)	
Alcohol drinking <sup>a</sup>			<0.001
No	253 (35.1)	15 (17)	
< 4 times/week	249 (34.5)	13 (14.8)	
$\geq$ 4 times/week	219 (30.4)	60 (68.2)	
Exercise <sup>a</sup>			0.88
No	410 (56.9)	48 (54.5)	
< 6 times/week	195 (27)	26 (29.5)	
$\geq$ 6 times/week	116 (16.1)	14 (15.9)	

<sup>a</sup>n (%). <sup>b</sup>Mann-Whitney U test or  $\chi^2$  test.

CHD, coronary heart disease; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase;  $\gamma$ -GTP, gamma glutamyltranspeptidase; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; TG, triglycerides; Hs-CRP, high-sensitivity C-reactive protein; HbA1c, haemoglobin A1c; HOMA-R, homeostasis model assessment.

The Spearman's correlation coefficients (Table 3) revealed a significantly positive relationship between carbohydrate intake (% energy) and 10-year CHD risk and an inverse relationship between fat intake (%

energy) and 10-year CHD risk.

Table 4 provides the crude and adjusted odds ratios for the predicted 10-year CHD risk in subjects by tertiles of dietary carbohydrate, protein, fat, and the ratio of n6/n3 fatty acid intakes. The logistic regression models showed that a significantly increased odds ratio (unadjusted) of the 10-year CHD risk was observed in the subjects with the highest tertile of daily carbohydrate intake (% energy) (odds ratio 3.64, 95% confidence interval [CI] 2.07–6.40); after adjustment for alcohol consumption, exercise, and the daily intakes of protein and fat, the odds ratio of the 10-year CHD risk was also higher in the subjects with the highest tertile of daily carbohydrate intake, although the results did not reach statistical significance (odds

**Table 3** Spearman's correlation coefficients between daily nutrient intakes and 10-year CHD risk

Variable	r	p
Energy	−0.020	0.575
Carbohydrate (% energy)	0.255	<0.001
Protein (% energy)	−0.039	0.273
Fatty (% energy)	−0.280	<0.001
Ratio of n-6/n-3 fatty acids	−0.172	<0.001

CHD, coronary heart disease.

**Table 2** Comparison of the estimated daily intakes of nutrients between the low-risk and high-risk groups

	10-year CHD risk		p
	<10% risk (n=721)	≥10% risk (n=88)	
Energy (kcal)	1,766 (587, 7,438)	1,704 (748, 2,693)	0.305
Carbohydrate (% energy)	55.5 (29.5, 77.7)	59.8 (41.9, 73.4)	<0.001
Protein (% energy)	13.4 (8.3, 24.1)	13.4 (7.9, 18.6)	0.788
Fatty (% energy)	30.9 (10.7, 47.8)	26.9 (15.7, 42.8)	<0.001
Ratio of n-6/n-3 fatty acids	4.78 (1.57, 9.15)	4.31 (2.55, 7.70)	<0.001

Data are expressed as median (minimum, maximum), and analyzed by Mann-Whitney *U* test.

CHD, coronary heart disease.

**Table 4** The unadjusted and adjusted odds ratios (95% CI) of 10-year CHD risk by tertiles of nutrient intakes

	Tertiles of estimated average nutrient intakes per day			p for trend
	Low	Intermediate	High	
Carbohydrate (% of energy), mean (n)	49.7 (274)	55.9 (270)	62.3 (265)	
Model 1 <sup>a</sup>	1.00	0.90 (0.45–1.80)	3.64 (2.07–6.40)**	<0.01
Model 2 <sup>b</sup>	1.00	0.72 (0.34–1.54)	1.72 (0.70–4.25)	0.236
Protein (% of energy), mean (n)	11.3 (266)	13.4 (279)	15.8 (264)	
Model 1 <sup>a</sup>	1.00	0.91 (0.54–1.56)	0.86 (0.50–1.49)	0.599
Model 2 <sup>c</sup>	1.00	1.21 (0.67–2.17)	1.32 (0.69–2.52)	0.407
Fat (% of energy), mean (n)	25.2 (268)	30.6 (270)	36.0 (271)	
Model 1 <sup>a</sup>	1.00	0.34 (0.20–0.58)**	0.16 (0.08–0.32)**	<0.01
Model 2 <sup>d</sup>	1.00	0.33 (0.18–0.61)**	0.15 (0.06–0.35)**	<0.01
Ratio of n-6/n-3 fatty acids, mean (n)	3.9 (270)	4.7 (270)	5.8 (269)	
Model 1 <sup>a</sup>	1.00	0.46 (0.27–0.78)**	0.32 (0.18–0.57)**	<0.01
Model 2 <sup>d</sup>	1.00	0.44 (0.25–0.79)**	0.31 (0.16–0.61)**	<0.01

CI, confidence interval; CHD, coronary heart diseases. \*\**p* < 0.01. Data were analyzed by multiple logistic regression analysis. Data in parentheses are 95% CI. <sup>a</sup>Not adjusted; <sup>b</sup>Adjusted for alcohol consumption, exercise, protein, and fat; <sup>c</sup>Adjusted for alcohol consumption, exercise, carbohydrate, and fat; <sup>d</sup>Adjusted for alcohol consumption, exercise, carbohydrate, and protein.

ratio 1.72; 95% CI 0.70–4.25).

We also found a significantly decreased dose-dependent odds ratio (unadjusted) for the 10-year CHD risk in the subjects with the increased fat intake (% energy) ( $p$  for trend  $< 0.01$ ) even after we controlled for alcohol consumption, exercise, and the daily intakes of carbohydrate and protein. The same tendency was also observed in the association of the ratio of n6/n3 fatty acids with the 10-year CHD risk both before and after adjustment for alcohol consumption, exercise, and the daily intakes of carbohydrate and protein ( $p$  for trend  $< 0.01$ ).

## Discussion

We found that carbohydrate intake (% energy) in the highest tertile ( $> 58.1\%$  total energy) were positively associated with the predicted 10-year CHD risk. There have been conflicting findings about the role of carbohydrate consumption in CHD risk [7, 12–19], although there is increasing evidence supporting an association between high dietary carbohydrate and CHD outcomes. Liu *et al.* reported that in a U.S. population, a high dietary glycemic index, glycemic load, and carbohydrate were risk factors for CHD in women but not men [26]. However, the authors of a recent large population study in the Netherlands reported that total carbohydrate and starch intakes were related to a higher CHD risk in men but not in women [27].

A large cohort study found a positive association between carbohydrate consumption and the risk of CHD in both adult men and women in Shanghai, China, where more than 60% of the total energy intake came from carbohydrate and 70% of the total carbohydrate was provided by white rice [28]. Daily rice intake is also high in Japan, accounting for about 43% of carbohydrate intake; a recent cohort study observed an inverse association between rice consumption and the risk of mortality from cardiovascular diseases in Japanese men but not in women [29]. Unfortunately, information about our subjects' rice intake was not available in our study; we only observed that the 10-year CHD risk tended to move upward as the total grain intake increased ( $p$ -trend  $< 0.01$ ) (data not shown).

It is known that high carbohydrate consumption increases TG and decreases HDL-c levels in the blood

[30–31], and that a low-fat, high carbohydrate diet might cause “a self-perpetuating insulin resistance state” and increase the risk of CHD [5–7]. Our present data showed that total grain intake was weakly and negatively correlated with the HDL-c level ( $r = -0.173$ ,  $p < 0.01$  by Spearman correlation analysis) but positively correlated with waist circumference ( $r = 0.200$ ,  $p < 0.01$ ) and the TG ( $r = 0.125$ ,  $p < 0.01$ ), AST ( $r = 0.220$ ,  $p < 0.01$ ), ALT ( $r = 0.239$ ,  $p < 0.01$ ), and  $\gamma$ -GTP levels ( $r = 0.245$ ,  $p < 0.01$ ) (data not shown).

In recent years, a short-term low-carbohydrate diet has been suggested to be effective for helping keep lost body weight off [32–34], but it is unclear whether a long-term carbohydrate-restricted diet is safe; some studies have found that a long-term low-carbohydrate diet was associated with a deficiency of micronutrients that caused mood disturbance, fatigue, headache, and skin rash [34]. It has been suggested that the carbohydrate intake should not be lower than 45% of the total energy to meet the glucose requirement of the brain and central nervous system [35].

We also found total fat intake (% energy) was inversely associated with the predicted 10-year CHD risk. There is insufficient evidence in the literature on the relationship between total fat consumption and CHD risk [7]. It has been suggested that total fat intake is not associated with CHD risk [6]. Most of the studies revealed a positive relationship between SFA intake and CHD risk [7], but we did not find such a relationship; rather, the level of saturated fat was low in the  $\geq 10\%$  CHD risk group (data not shown). The possibility that individuals who had higher levels of blood TC, TG, and LDL-c or who were obese had changed their dietary habits or paid more attention to their diets cannot be excluded. In addition, a recent study in Japan did not find any association between SFAs and mortality from heart disease [18]. The present findings need to be confirmed in future investigations of general populations.

The present findings revealed by the logistic analysis also indicated a dose-dependently decreased odds ratio of 10-year CHD risk in the subjects with the increased ratio of n6/n3 fatty acid intake, even after we controlled for alcohol consumption, exercise, and the daily intakes of carbohydrate and protein. Both n6 and n3 are essential fatty acids, and humans and animals cannot synthesize them; they must gain them from their diet. In Europe and the U.S., the ratio of

n6/n3 fatty acid intake, especially n6 intake, is quite high, which is believed to be related to the mortality from cardiovascular disease, and a decrease in the n6/n3 ratio in the diet resulted in reductions of platelet aggregation in coronary arteries and in the serum levels of vascular endothelial growth factor [36].

However, Charnock [37] suggested that high n6 consumption probably decreases the risk of sudden death by increasing the threshold for ventricular arrhythmias. In Japan, the average ratio of n6/n3 fatty acid intake is about 1/3 of that in Europe and the U.S. High n3 intake (with high concentration in fish) is thought to contribute to the prevention of fatal CHD and sudden cardiac death, but the preventive effects of n3 were inconclusive for nonfatal CHD [6, 38–40]. It has been suggested that the balance of n6 and n3 fatty acid intakes is rather important in the prevention of CHD [6, 36], a concept which may provide support for our present findings.

This study has a number of limitations. (1) This analysis was based on data from one prefecture in Japan (similar to a state in the U.S.), and the sample size was small; therefore, caution should be taken to avoid generalizing the present findings. (2) The data on lifestyles were gathered via self-reporting, which might be subject to recall bias. (3) The intakes of carbohydrate, protein, fat, and n6/n3 fatty acids were estimated using a food frequency questionnaire. This choice may have weakened the magnitude of the association between the intakes of macronutrients and the 10-year CHD risk due to the presence of a fixed list of foods and food groups, variation in the interpretation of dietary questions (4) The cross-sectional nature of the study indicates that we cannot examine the causality of the daily consumption of carbohydrate, protein, and fat regarding the 10-year CHD risk among the subjects. (5) Framingham risk scoring is the most widely used CHD risk estimation system in the world [41]; it was derived from a general population in the U.S. [20]. Since the mortality and morbidity of heart disease for adults are higher in the U.S. compared to in Japan, the present results must be interpreted cautiously.

In conclusion, the present findings add evidence of a positive association of dietary carbohydrate and inverse associations of total fat and n6/n3 fatty acid ratio with the predicted 10-year CHD risk in a general Japanese population. A study using a longitudinal

design with a large sample size is necessary to verify the present results.

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