Table 1
Potential confounding variables according to alcohol use ($n = 3225$)

| Variable | Never use | Past use | Alcohol (ml per day) | | |
|---|---|---|---|---|---|
| | | | <30 | 30–59 | 60+ |
| Number | 455 | 96 | 815 | 923 | 936 |
| Parental history of diabetes (%) | 9.7 | 17.7 | 9.5 | 9.5 | 8.9 |
| BMI (kg/m$^2$), mean (S.D.) | 24.1 (2.8) | 24.0 (3.3) | 23.9 (2.7) | 23.9 (2.5) | 23.8 (2.5) |
| Current smoking (%) | 52.1 | 52.1 | 38.7 | 46.5 | 53.2 |
| Number of cigarettes per day, median (IQR)[a] | 20 (20–30) | 20 (20–30) | 20 (20–25) | 20 (20–25) | 20 (20–30) |
| METs-hour per week, median (IQR) | 10 (0–24) | 12 (0–27) | 16 (6–28) | 16 (6–28) | 16 (5–28) |

S.D.: standard deviation; IQR: interquartile range.
[a] Current smokers only.

SDF, parental history of diabetes, BMI, leisure-time physical activity, and alcohol intake or cigarette smoking. Age was in a limited range from 46 to 59 years, and 98% of the subjects were aged 50–54 years. Thus age was omitted in the present analysis. The 95% confidence interval (CI) of OR was estimated by using the standard error of a logistic regression coefficient for each indicator variable.

Alcohol use was categorized into five groups (never, past, and current drinking with a consumption of <30, 30–59, or 60+ ml of alcohol per day). Cigarette smoking was categorized into five categories (never, past, and current smoking with a consumption of <15, 15–24, or 25+ cigarettes per day). BMI was classified at the cut off points of the 25, 50, and 75th percentiles in the distribution. Rank in the SDF was divided into three classes (low, middle, or high), and leisure-time physical activity into four levels (no regular exercise and tertiles of MET-hours per week in regular participants). Indicator variables representing categories of the above-mentioned factors were included in the logistic regression models as independent variables.

The trend of the association with alcohol use or cigarette smoking was assessed by using multiple logistic regression with ordinal scores (0, 1, 2, and 3) assigned to four levels of alcohol use or cigarette smoking after exclusion of past drinkers or past smokers. Two-sided $p$ values less than 0.05 were regarded as statistically significant. All analyses were performed using the Statistical Analysis System (SAS) version 6.12 (SAS Institute, Inc., Cary, NC).

## 3. Results

Of the 3038 men, there were 204 (7%) prevalent cases of IFG, 568 (19%) of IGT, 171 (6%) of newly diagnosed type 2 diabetes mellitus.

Table 1 shows distributions of the covariates according to categories of alcohol use. Current smoking was more frequent with increasing levels of alcohol consumption. Physical exercise during leisure-time was greater in current drinkers than in never and past drinkers. Neither parental history nor BMI was measurably correlated with alcohol use. On the other hand, mean BMI was lower in current smokers regardless of the number of cigarette per day. Physical exercise during leisure-time decreased progressively with increasing levels of cigarette smoking (Table 2).

Table 3 presents adjusted ORs of IFG, IGT, and type 2 diabetes mellitus each in relation to levels of alcohol drinking and cigarette smoking. Alcohol use was positively associated with IFG, IGT, and type 2 diabetes mellitus each with a statistically significant trend. The ordinal ORs of glucose intolerance increased gradiently with increasing amounts of alcohol intake. Cigarette smoking was not measurably related to any of the three categories of glucose intolerance. Nor did the ordinal

Table 2
Potential confounding variables according to cigarette smoking category ($n = 3225$)

| Variable | Never smoking | Past smoking | No. of cigarettes per day | | |
|---|---|---|---|---|---|
| | | | <15 | 15–24 | 25+ |
| Number | 841 | 855 | 100 | 920 | 509 |
| Parental history of diabetes (%) | 8.8 | 10.2 | 9.0 | 9.0 | 11.0 |
| BMI (kg/m$^2$), mean (S.D.) | 24.1 (2.4) | 24.2 (2.4) | 23.5 (3.1) | 23.6 (2.8) | 23.6 (2.7) |
| Current alcohol use (%) | 80.4 | 88.4 | 84.0 | 81.6 | 80.0 |
| Alcohol (ml per day), median (IQR)[a] | 36 (18–61) | 46 (27–72) | 45 (19–72) | 47 (27–72) | 58 (35–90) |
| METs-hour per week, median (IQR) | 16 (7–29) | 17 (7–29) | 16 (5–32) | 13 (3–26) | 10 (0–22) |

S.D.: standard deviation; IQR: interquartile range.
[a] Current alcohol users only.

Table 3
Adjusted odds ratios and 95% confidence intervals of glucose tolerance status according to alcohol use and cigarette smoking

| Variable | No. of controls | IFG | | IGT | | Type 2 diabetes mellitus | | Ordinal class of glucose intolerance | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | OR (95% CI)[a] | No. | OR (95% CI)[a] | No. | OR (95% CI)[a] | No. | OR (95% CI)[a] |
| Alcohol (ml per day) | | | | | | | | | |
| Never use | 340 | 14 | 1.00 (referent) | 65 | 1.00 (referent) | 10 | 1.00 (referent) | 89 | 1.00 (referent) |
| Past use | 61 | 5 | 2.12 (0.72–6.18) | 13 | 1.08 (0.55–2.09) | 6 | 3.27 (1.12–9.54) | 24 | 1.56(0.92–2.63) |
| <30 | 536 | 40 | 1.86 (0.99–3.51) | 136 | 1.38 (0.99–1.93) | 50 | 3.70 (1.83–7.50) | 226 | 1.78 (1.34–2.36) |
| 30–59 | 588 | 62 | 2.50 (1.36–4.58) | 173 | 1.59 (1.15–2.20) | 48 | 3.16 (1.56–6.41) | 283 | 1.94 (1.47–2.56) |
| 60+ | 570 | 83 | 3.57 (1.98–6.46) | 181 | 1.75 (1.27–2.42) | 57 | 3.93 (1.96–7.91) | 321 | 2.25 (1.71–2.96) |
| Trend[b] | | | $p < 0.0001$ | | $p = 0.0005$ | | $p = 0.002$ | | $p < 0.0001$ |
| Cigarettes per day | | | | | | | | | |
| Never smoking | 583 | 51 | 1.00 (referent) | 133 | 1.00 (referent) | 42 | 1.00 (referent) | 226 | 1.00 (referent) |
| Past smoking | 524 | 67 | 1.29 (0.87–1.91) | 173 | 1.37 (1.05–1.78) | 43 | 1.04 (0.66–1.63) | 283 | 1.24 (1.01–1.54) |
| <15 | 62 | 6 | 1.24 (0.50–3.08) | 16 | 1.18 (0.65–2.14) | 9 | 2.17 (0.98–4.80) | 31 | 1.47 (0.93–2.32) |
| 15–24 | 595 | 58 | 1.13 (0.75–1.70) | 161 | 1.21 (0.93–1.57) | 45 | 1.15 (0.73–1.80) | 264 | 1.16 (0.94-1.44) |
| 25+ | 331 | 22 | 0.78 (0.46–1.34) | 85 | 1.11 (0.81–1.52) | 32 | 1.33 (0.80–2.20) | 139 | 1.12 (0.87–1.45) |
| Trend[c] | | | $p = 0.46$ | | $p = 0.26$ | | $p = 0.40$ | | $p = 0.29$ |

OR: odds ratio; CI: confidence interval.
[a] Adjusted for hospital, rank, parental history of diabetes, BMI, leisure-time physical activity, and either alcohol intake or smoking.
[b] Past drinkers were excluded.
[c] Past smokers were excluded.

logistic regression analysis show an appreciable association between smoking and glucose intolerance.

## 4. Discussion

The present study showed positive associations of alcohol use with IFG, IGT, and type 2 diabetes mellitus independent of BMI, physical activity, and other confounding factors. Increased ORs of IFG, IGT and type 2 diabetes mellitus were observed not only in heavy drinkers but also in light (<30 ml per day) and moderate (30–59 ml per day) drinkers. The present findings suggest that alcohol use may be related to an increased risk of type 2 diabetes mellitus.

A fairly large number of prospective studies have addressed the relation between alcohol use and type 2 diabetes mellitus, but their findings are inconsistent [7–18]. Inconsistency is noted even among studies in Japan [7,11,17,18]. Two studies of Japanese showed a decreased risk for the consumption of 30–50 g in alcohol per day [7,11], the other two reported a positive association between alcohol use and type 2 diabetes mellitus [17,18]. A decrease in the risk of type 2 diabetes mellitus was observed not only in those with moderate consumption (10–49 g per day) but also in those with a relatively high consumption (≥50 g per day) in the Health Professional Follow-Up Study in the United States [8]. On the contrary, a community-based prospective study in the United States reported an evident increase in the risk of type 2 diabetes mellitus diagnosed by the glucose tolerance test in men with a high alcohol consumption (≥25 g per day), but not in women classified as those with high alcohol consumption (≥17 g per day) [14]. In Hispanic Americans [15], each consumption of 10 g in alcohol per week was associated with more than two-fold increase in the risk of developing type 2 diabetes mellitus in men but not in women. Another prospective study in the United States also reported a significantly increased risk of type 2 diabetes mellitus in men consuming 40 g or more alcohol per day as compared with the moderate drinkers (9–18 g per day) [16].

The inconsistency regarding alcohol use and type 2 diabetes mellitus in these prospective studies does not seem to be ascribed to different criteria for type 2 diabetes mellitus in different studies. The findings are disparate even among studies based on the same methods such as the American Diabetes Association criteria for fasting plasma glucose [7,11,16] and self-reported physician's diagnosis [8,9,18]. Furthermore, important confounding factors such as BMI and physical activity were adjusted for in most of the studies. The present study was cross-sectional in design, and thus the findings are less convincing as compared with those from the previous prospective studies. However, 75-g OGTT was used for determination of glucose tolerance status. Two of the three previous cross-sectional studies based on a 75-g OGTT found a

significant positive association between alcohol use and type 2 diabetes mellitus [24,25], and the other found no measurable association [23]. Further studies are needed to clarify the association between alcohol and type 2 diabetes mellitus.

The above-mentioned three studies also examined the relation between alcohol use and IGT [23–25]. Moderate alcohol drinking was related to a decreased risk of IGT among Swedish men [24], but the other two studies failed to find any significant association [23,25]. In the present study, increased ORs associated with alcohol use were seemingly greater for IFG and type 2 diabetes mellitus than for IGT. This may have been due to chance fluctuation, because the 95% CIs of ORs well overlapped among the three categories of glucose intolerance.

Biological mechanisms regarding alcohol and glucose intolerance also remain unclear. Although some epidemiological and experimental studies suggested a beneficial effect of moderate alcohol use on insulin sensitivity [3,4], others failed to find such a beneficial effect [5,6]. Alcohol use was shown to exert a direct toxic rather than beneficial effect on the pancreas, and thereby yielding a defect in insulin secretion in animals [31,32], and alcohol was also shown to decrease glucose utilization in healthy men [33]. A recent study has noted a distinct difference in the insulin profile after glucose challenge between IFG and IGT [34]. Insulin resistance is a characteristic feature of IFG, while impaired insulin secretion is observable in individuals with IGT [34]. It is of interest to examine the insulin profile during the OGTT in relation to alcohol intake, but no such data were available in the present study.

In the present study, smoking was not clearly associated with any categories of glucose intolerance. Recently, several prospective studies have reported a positive association between cigarette smoking and type 2 diabetes mellitus [9,19–21]. In two studies, the increased risk was observed in the consumption of 15 or more cigarettes per day, but the increased risk was modest among current smokers with the consumption of 25 or more cigarettes per day [19,20]. On the other hand, the consumption of 31 or more cigarettes per day was associated with more than four-fold increase in the risk of developing type 2 diabetes mellitus in Japanese men [21]. In the Nurses' Health Study, an increase in the risk of type 2 diabetes mellitus was observed in those with a relatively light consumption (1–14 cigarettes per day) [9]. We have no clear explanation for the lack of association between smoking and type 2 diabetes mellitus in the present study.

The present study had several methodological advantages other than the use of 75-g OGTT. The number of subjects was fairly large, and the subjects were homogeneous in terms of social background as well as age range. Since the preretirement health examination program covered almost all men retiring from the Self-Defense Forces, selection bias was negligible. Lifestyles were ascertained before the results of medical examination were reported, and it is unlikely that men with glucose intolerance had changed their lifestyles. Although men with a history of dietary or drug treatment for diabetes mellitus were excluded, part of the study subjects may have been informed of hyperglycemia previously, because the annual health check-up including urine glucose test or measurement of fasting plasma glucose has been carried out in the Self-Defense Forces, as done at workplaces elsewhere in Japan. It is, however, unlikely that such individuals who were probably at high risk of glucose intolerance had increased alcohol consumption. Weakness of the cross-sectional study should be borne in mind when interpreting the present results, as mentioned above. Our study subjects were men serving for the SDF until retirement. The study subjects may differ from men in the general population in various lifestyle aspects. Our findings thus may not be directly generalized for the general population.

In conclusion, a cross-sectional study based on a 75-g OGTT showed a positive association between alcohol use and glucose intolerance and a null association between smoking and glucose intolerance. The role for alcohol use and smoking in the development of type 2 diabetes mellitus needs further clarification.

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# Dietary Patterns and Glucose Tolerance Abnormalities in Japanese Men[1]

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ABSTRACT The Western dietary pattern appears to confer diabetes risk, but the role of dietary patterns in Asian populations remains unclear. We investigated the association between major dietary patterns and the glucose tolerance status of Japanese men. Abnormalities included impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes. Subjects were 2106 Japanese men who were administered a 75-g oral glucose tolerance test at their preretirement health check-ups. Information about diet was obtained using a 74-item FFQ before the test. Three dietary patterns were generated by factor analysis: *1*) a high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern; *2*) an animal food pattern; and *3*) a Japanese pattern. We used logistic regression analysis to estimate odds ratios (OR) with adjustment for potential confounding variables. A significant inverse association was found for the high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern ($P$ for trend $< 0.0001$); the OR of having a glucose tolerance abnormality (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes) for the 2nd, 3rd, and 4th quartiles were 0.80 (95% CI = 0.62–1.04), 0.71 (95% CI = 0.54–0.92), and 0.51 (95% CI = 0.38–0.67), respectively, compared with the lowest quartile. The inverse association was consistent for each glucose tolerance abnormality as well as across subgroups stratified by risk factors for diabetes. The Japanese dietary pattern was positively associated with impaired glucose tolerance ($P$ for trend = 0.048). A dietary pattern characterized by frequent consumption of dairy products and fruits and vegetables but low alcohol intake may be associated with a decreased risk of developing a glucose tolerance abnormality. J. Nutr. 136: 1352–1358, 2006.

KEY WORDS: • *dietary pattern* • *factor analysis* • *impaired fasting glucose* • *impaired glucose tolerance* • *type 2 diabetes*

The prevalence of type 2 diabetes is increasing worldwide (1). A recent Japanese survey showed that 9% of the adult population have known or suspected diabetes, and another 11% may also have diabetes (2). The age-specific prevalence of diabetes in Japanese subjects is slightly higher than that in European populations (3,4). The results of these surveys seem peculiar in light of the fact that obesity is not as prevalent in Japanese patients with type 2 diabetes as in Caucasian patients (5). This may be attributable in part to a high genetic susceptibility to type 2 diabetes of Japanese individuals (6); however, little is known about the role of diets typically consumed by the Japanese.

Analysis of dietary patterns has received much attention as a method of investigating the role of diet in studies of chronic diseases. Approaches of this sort, focusing on a combination of several foods, can overcome problems arising from the close intercorrelation and potential effect modulation among numerous foods or nutrients (7,8). Of factor-analysis studies among Western populations (9–12), some (11,12) indicated that a Western dietary pattern characterized by a greater consumption of high-energy, high-fat foods predicts diabetes risk. However, dietary patterns generated by factor analysis may differ across populations with different dietary cultures. The high consumption of rice, fish, and soybean products in Japan (13) suggests several different dietary patterns in Japanese populations.

The aim of the present study was therefore to investigate dietary patterns in relation to glucose tolerance status, using data from preretirement health examinations of Japanese men who were self-defense officials.

## SUBJECTS AND METHODS

*Study procedure.* The data used were derived from the Self-Defense Forces Health Study, a cross-sectional survey of men who were self-defense officials and participated in a preretirement health check-up at 2 hospitals (Fukuoka and Kumamoto) in Japan. The study procedure was described elsewhere (14–16). Study questionnaires regarding smoking, drinking, leisure-time physical activity, diet, and other health-related information were distributed before the test to male examinees on d 1 of hospital admission for examination. For leisure-time physical activity, the men were asked about the weekly

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frequency and the duration of each activity on each occasion for up to 3 types of activity. Research assistants checked the questionnaire and, if necessary, sought clarification from the study subjects. Results of physical measurements and laboratory tests were extracted from clinical reports. Written informed consent was obtained from study participants. The study protocol was approved by the ethics committee of Kyushu University.

***Study subjects.*** Among 2377 male self-defense officials who underwent the examination from April 1999 through March 2002, 2370 men aged 47–59 y (mean, 52.4 y) agreed to participate in the study. After excluding men with a history of cancer, stroke, myocardial infarction, coronary revascularization, inflammatory bowel diseases, colorectal surgery, or diabetes mellitus, 2141 men were included for the analysis of dietary patterns. After further exclusion of 35 men who had a history of gastrectomy, a condition that might affect the oral glucose tolerance test result, we analyzed the data for the remaining 2106 men to assess the association between dietary patterns and glucose tolerance status.

***Glucose measurements.*** All officials undergo a comprehensive health examination before retirement; the exam includes a 75-g oral glucose tolerance test as a routine procedure. After an overnight fast, venous blood was drawn for measurement of plasma glucose before and 2 h after the oral glucose load. Examinees whose fasting plasma glucose concentration at admission was ≥7.0 mmol/L or who were under medical care for diabetes were not given an oral glucose tolerance test. Plasma glucose concentrations were measured by the glucose oxidase method using commercial reagents (Shino Test).

***Dietary assessment.*** Information about diet was collected using a FFQ designed to assess the average intake of 74 foods, food groups, and food preparations over the previous year. The questionnaire was an expanded version of a 45-item FFQ that was developed on the basis of a published questionnaire (17) and was validated against four 7-d records, collected each season (18). The expansion of food items was done with reference to food consumption in the National Nutrition Survey (13) and a dietary questionnaire developed elsewhere in Japan (19). Participants were asked to choose from 7 response options for most dietary items, ranging from "never/<1 time/mo" to "2–3 times/d." Different response schemes were used for green tea, coffee, and rice (5 options), and alcoholic beverages (6 options). Daily consumers of green tea, coffee, or rice were asked about the number of cups or bowls consumed per day. Current drinkers, defined as those who consumed alcoholic beverages weekly for at least 1 y in their lifetime and who were drinking at the time of the survey, were asked about the frequency of consumption and the amount consumed per occasion of 5 alcoholic beverages, that is, sake (a Japanese wine), shochu (a Japanese distilled beverage), beer, whiskey, and wine. The amount consumed per occasion was used in the estimation of total ethanol intake from these alcoholic beverages, but only the frequency of consumption for each alcoholic beverage was used in the analysis of dietary patterns.

Before the analysis of dietary patterns, intakes of green tea, coffee, or rice were converted into units of cups or bowls per day, whereas those of other dietary items were quantified in terms of frequency per week. Five dietary questions that overlapped with or were duplicated by others (collective consumption of cooked vegetables, apple, tangerine, other orange, watermelon) and 3 questions about food spreads (butter, margarine, and jam/honey) were not included. Furthermore, some foods or food groups similar in nutritional contents or culinary use were combined (**Appendix 1**), leaving 39 food items for purposes of the present study.

***Statistical analysis.*** The method used in generating dietary patterns and the naming of the derived patterns were described in our previous study of colorectal adenomas (16). Dietary patterns were generated by factor analysis (principal components). Factor analysis is a technique used to reduce a number of variables into fewer independent factors. To simplify interpretation, a linear transformation called a "rotation" is normally performed on the initial factor solution. We used an orthogonal rotation procedure (varimax rotation), which maintains the uncorrelated nature of the factors. In determining the number of factors to retain, we considered the scree test and interpretability. The scree plot and postrotated factor loadings revealed that 3 factors described comprehensively the distinctive dietary patterns of the study population. We thus retained the 3 patterns and designated them as follows: *1*) a high-dairy, high-starch, high-fruit and -vegetable, low-alcohol (DSFA)[3] pattern; *2*) an animal food pattern; and *3*) a Japanese pattern, according to the food items showing high loading (absolute value) with respect to each dietary pattern (**Table 1**). We confirmed that these dietary factors emerged when all 74 food items in our questionnaire were simply included in factor analysis and that patterns of loading with the dietary factors were similar among foods or food groups combined. A factor score for each dietary pattern was calculated by weighting standardized consumption of each food item by the corresponding factor loading and summing the resulting values. This score ranked individuals in terms of how closely they conformed to the dietary pattern.

The potential confounding variables considered were hospital (Fukuoka or Kumamoto), age (treated as a continuous variable), parental history of diabetes (absent or present), occupational rank (3 categories), BMI (continuous), smoking (lifetime nonsmoker, former smoker, and current smoker using <15, 15–24, or ≥25 cigarettes/d), and leisure-time physical activity, expressed as the sum of metabolic equivalents (MET) for each activity multiplied by the corresponding hours of such activity per week (none, <20, 20–39.9, or ≥40 MET-h/wk). Subjects were classified as having impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes, according the 1998 WHO diagnostic criteria (20). These 3 conditions combined were referred to in this paper to as the "glucose tolerance abnormality." Multiple logistic regression that included terms for the above-mentioned variables was performed to estimate the odds ratio (OR) and 95% CI of each study outcome according to quartiles of scores for each dietary pattern, taking the lowest quartile group as the reference group. In the analysis of specific outcomes, i.e., impaired glucose tolerance, impaired fasting glucose, or diabetes, data for those with the other types of glucose tolerance abnormalities were excluded. Trend association was assessed by assigning a median score to each quartile for each dietary pattern. Analyses were repeated after stratification of known risk or preventive factors for diabetes including obesity, parental history of diabetes, smoking, and leisure-time physical activity. Statistical significance of the interactions between dietary pattern (as a continuous variable) and the stratified variables was assessed by the Wald $\chi^2$ statistic. All analyses were done using SAS version 8.2 (21).

## RESULTS

Factor loadings are equivalent to simple correlations between the food items and the dietary patterns. A positive loading indicates that the food item is positively associated with the dietary pattern, and a negative loading indicates an inverse association with the dietary pattern. The DFSA dietary pattern was characterized by frequent intake of fermented dairy products, milk, confectioneries, bread, fruits, and vegetables, and infrequent intake of shochu, a local alcoholic beverage in the study area (Table 1). The animal food dietary pattern was characterized by various kinds of animal foods, including red meat, poultry, seafood excluding fish, processed meat and fish products, and fried or broiled foods. The Japanese dietary pattern was characterized by foods traditionally consumed in Japan (soybean products, seaweeds, pickles, and green tea), vegetables, and fish. The proportion of the total variance explained by the 3 factors was 24%.

The 3 dietary patterns were related to some of the potential confounding variables and alcohol consumption (**Table 2**). Examinees at Kumamoto hospital had a higher score for the Japanese dietary pattern but lower scores for the DFSA and animal food dietary patterns than those at Fukuoka hospital. Men with a higher score for the DFSA dietary pattern engaged in higher levels of leisure-time physical activity and consumed smaller amounts of alcohol; in addition, they had a higher

[3] Abbreviations used: DASH, Dietary Approaches to Stop Hypertension; DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern); MET, metabolic equivalent; OR, odds ratio.

**TABLE 1**

*Factor loading matrix for dietary patterns*[1]

| | DFSA dietary pattern | Animal food dietary pattern | Japanese dietary pattern |
|---|---|---|---|
| Fermented dairy products | 0.61 | — | — |
| Confectionary | 0.55 | 0.18 | — |
| Canned/dried fruits | 0.52 | — | — |
| Bread | 0.47 | — | −0.39 |
| Fruits, not canned/dried | 0.47 | — | 0.21 |
| Fruits juice | 0.47 | — | — |
| Vegetable juice | 0.41 | — | 0.17 |
| Milk | 0.40 | — | — |
| Dressing oil | 0.33 | 0.19 | 0.26 |
| Soda, cola | 0.30 | 0.20 | −0.18 |
| Shochu (alcoholic beverage) | −0.40 | 0.15 | 0.24 |
| Red meat | — | 0.68 | — |
| Poultry | — | 0.63 | — |
| Fried foods | 0.25 | 0.49 | 0.29 |
| Broiled fish/broiled meat, all kinds | — | 0.48 | 0.32 |
| Seafood, except fish | — | 0.47 | 0.18 |
| Processed meat | 0.17 | 0.46 | — |
| Processed fish | — | 0.41 | 0.18 |
| Gyoza[2] | — | 0.40 | — |
| Liver | — | 0.38 | — |
| Egg | — | 0.34 | 0.22 |
| Noodle | — | 0.34 | — |
| Soybean products | — | — | 0.64 |
| Cooked vegetables | 0.36 | 0.23 | 0.56 |
| Seaweeds | 0.27 | — | 0.55 |
| Raw vegetables | 0.45 | — | 0.52 |
| Pickles | 0.19 | — | 0.51 |
| Green tea | — | −0.15 | 0.46 |
| Fish | — | 0.27 | 0.38 |
| Potato | 0.33 | 0.24 | 0.35 |
| Garlic | 0.20 | — | 0.32 |
| Variance explained, % | 8.5 | 7.9 | 7.7 |

[1] Factor loadings less than ± 0.15 were represented by a dash for simplicity; food items with factor loadings less than ± 0.30 for all dietary patterns (rice, mayonnaise, nuts, coffee, wine, beer, whisky, sake) were omitted.

[2] Dumpling with minced pork and vegetable stuffing.

proportion of nonsmokers than those with a lower score. Men with a higher score for the animal food dietary pattern had higher BMI and consumed larger amounts of alcohol. Men with a higher score for the Japanese dietary pattern engaged in higher levels of leisure-time physical activity, consumed greater amounts of alcohol, and had a higher proportion of nonsmokers than those with a lower score.

A total of 151, 384, and 112 men were identified as having impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes, respectively. The DFSA dietary pattern was significantly, inversely associated with glucose tolerance abnormalities, with men in the highest quartile of the dietary pattern having an OR that was half that of those in the lowest quartile (**Table 3**). The inverse association was consistent for impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes, although the pattern of decreasing trend differed somewhat among them. The Japanese dietary pattern showed a significant, positive trend association with impaired glucose tolerance ($P$ for trend = 0.048); compared with the lowest quartile of the pattern, the OR for the upper 3 quartiles combined was 1.37 (95% CI = 1.03–1.82). No apparent trend association was observed for the animal food dietary pattern.

The association between the DFSA dietary pattern and glucose intolerance was further examined according to factors associated with type 2 diabetes (**Table 4**). Overall, the inverse association was consistent across subgroups stratified by the factors. However, some variations in the pattern of the association were observed; there was a large reduction in OR between the lowest (reference) and 2nd quartiles of the DFSA dietary pattern among individuals who had a larger body mass, whereas the OR gradually decreased as the dietary pattern score increased among those who had a normal body mass ($P$ for interaction < 0.001). Such differences in patterns were also observed when the association was stratified by parental history of diabetes, although the interaction was not significant ($P$ for interaction = 0.67).

## DISCUSSION

We investigated the association between major dietary patterns and glucose tolerance status among middle-aged Japanese men. Of the 3 dietary patterns we identified, the DFSA dietary pattern had a significant, inverse association with glucose tolerance abnormalities or with each diagnostic subcategory. Additionally, the inverse association was consistent across subgroups stratified according to known factors predictive of diabetes.

Our study has several strengths. Glucose tolerance status was determined on the basis of an oral glucose tolerance test. Selection bias in terms of study participation was unlikely because of nonselective recruitment for the preretirement health

## TABLE 2

*Potential confounding variables and alcohol consumption by quartiles of dietary patterns in Japanese men*

| Dietary pattern | Hospital, % *Kumamoto* | Age, *mean y* | Rank, % *highest* | Parental history of diabetes, % | BMI, *mean kg/m²* | Smoking, *% current* | Leisure-time physical activity, *median MET-h/wk* | Alcohol,[1] *median mL/d* |
|---|---|---|---|---|---|---|---|---|
| DFSA dietary pattern | | | | | | | | |
| Quartile 1 (low) | 44 | 52.4 | 11 | 6 | 23.9 | 52 | 14.5 | 62 |
| Quartile 2, 3 | 38 | 52.4 | 13 | 9 | 23.8 | 46 | 16 | 36 |
| Quartile 4 (high) | 31 | 52.4 | 18 | 12 | 23.7 | 44 | 16 | 14 |
| *P* for trend[2] | <0.001 | 0.32 | <0.001 | <0.001 | 0.20 | <0.01 | 0.02 | <0.001 |
| Animal food dietary pattern | | | | | | | | |
| Quartile 1 (low) | 42 | 52.4 | 15 | 8 | 23.6 | 48 | 16 | 22 |
| Quartile 2, 3 | 38 | 52.4 | 14 | 9 | 23.8 | 48 | 16 | 39 |
| Quartile 4 (high) | 33 | 52.4 | 12 | 10 | 24.0 | 45 | 14 | 48 |
| *P* for trend | <0.01 | 0.20 | 0.15 | 0.14 | 0.01 | 0.28 | 0.41 | <0.001 |
| Japanese dietary pattern | | | | | | | | |
| Quartile 1 (low)30 | | 52.4 | 18 | 9 | 23.8 | 52 | 10.5 | 23 |
| Quartile 2, 3 | 39 | 52.4 | 13 | 8 | 23.8 | 46 | 16 | 43 |
| Quartile 4 (high) | 43 | 52.4 | 11 | 11 | 23.9 | 44 | 18 | 45 |
| *P* for trend | <0.001 | 0.32 | 0.001 | 0.17 | 0.64 | <0.01 | <0.001 | <0.001 |

[1] Estimated from the consumption of 5 alcoholic beverages: beer, sake, shochu, wine, and whisky.
[2] Mantel-Haenszel $\chi^2$ test for categorical variables; linear regression analysis for continuous variables, assigning ordinal score to each category; leisure-time physical activity and alcohol consumption data were log-transformed.

examination and high study participation rate. The questionnaire was distributed and collected before the oral glucose tolerance test, and the data for subjects with a history of diabetes were excluded; thus, recall bias associated with glucose tolerance status was also unlikely. We controlled for major known or suspected confounding factors. Moreover, because the study participants were homogeneous in terms of occupation, sex, and age, the results were less likely to be biased by unknown or unmeasured confounding factors.

The present study also has some limitations. According to the validation study for the former version of the dietary questionnaire (14), including questions and response options similar to those of the current questionnaire, most nutrients and foods demonstrated fairly good correlation between the dietary record and the questionnaire; the correlation coefficients ($r$) of 0.80, 0.77, and 0.58 for bread, fruits, and dairy products, major food items of the DFSA dietary pattern, were relatively high. Therefore, bias associated with nondifferential misclassification in dietary assessment may be minimal for the analysis of the DFSA dietary pattern. On the other hand, the correlation between the dietary record and the questionnaire was moderate for meat ($r = 0.48$), poultry ($r = 0.59$), fish ($r = 0.51$), fermented soybean ($r = 0.52$), and vegetables ($r = 0.40$), and this may be a reason for the lack of an apparent association for the animal food or Japanese dietary patterns. Another issue regarding dietary assessment is that the calculation and

## TABLE 3

*OR of having glucose tolerance abnormality by quartiles of dietary patterns in Japanese men*

| | Quartile | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 2 | | 3 | | 4 (high) | | |
| Dietary pattern | 1 (low) | OR[2] | 95%CI | OR | 95%CI | OR | 95%CI | *P* for trend |
| Glucose tolerance abnormality[1] ($n$ = 647) | | | | | | | | |
| DFSA dietary pattern | 1.00 | 0.80 | 0.62–1.04 | 0.71 | 0.54–0.92 | 0.51 | 0.38–0.67 | <0.0001 |
| Animal food dietary pattern | 1.00 | 1.15 | 0.88–1.51 | 0.89 | 0.67–1.16 | 0.97 | 0.74–1.27 | 0.43 |
| Japanese dietary pattern | 1.00 | 1.14 | 0.86–1.50 | 1.40 | 1.06–1.83 | 1.20 | 0.91–1.58 | 0.14 |
| Impaired fasting glucose ($n$ = 151) | | | | | | | | |
| DFSA dietary pattern | 1.00 | 1.00 | 0.63–1.59 | 0.94 | 0.59–1.50 | 0.54 | 0.32–0.91 | 0.02 |
| Animal food dietary pattern | 1.00 | 0.98 | 0.61–1.58 | 0.85 | 0.52–1.37 | 0.99 | 0.62–1.59 | 0.87 |
| Japanese dietary pattern | 1.00 | 0.98 | 0.59–1.60 | 1.28 | 0.79–2.06 | 0.90 | 0.54–1.49 | 0.85 |
| Impaired glucose tolerance ($n$ = 384) | | | | | | | | |
| DFSA dietary pattern | 1.00 | 0.70 | 0.51–0.96 | 0.62 | 0.45–0.85 | 0.50 | 0.36–0.70 | <0.0001 |
| Animal food dietary pattern | 1.00 | 1.18 | 0.86–1.63 | 0.77 | 0.55–1.08 | 1.02 | 0.74–1.41 | 0.59 |
| Japanese dietary pattern | 1.00 | 1.25 | 0.89–1.75 | 1.50 | 1.07–2.10 | 1.39 | 0.99–1.94 | 0.048 |
| Diabetes mellitus ($n$ = 112) | | | | | | | | |
| DFSA dietary pattern | 1.00 | 0.92 | 0.54–1.55 | 0.71 | 0.41–1.22 | 0.50 | 0.28–0.91 | 0.01 |
| Animal food dietary pattern | 1.00 | 1.54 | 0.87–2.70 | 1.58 | 0.91–2.75 | 0.73 | 0.38–1.40 | 0.33 |
| Japanese dietary pattern | 1.00 | 1.03 | 0.59–1.80 | 1.27 | 0.73–2.20 | 0.96 | 0.54–1.69 | 1.00 |

[1] Including impaired fasting glucose, impaired glucose tolerance, and diabetes mellitus.
[2] OR adjusted for hospital, age, occupational rank, parental history of diabetes, BMI, smoking, and leisure-time physical activity.

## TABLE 4

*OR of having glucose tolerance abnormality by quartiles of the DFSA dietary patterns, according to risk factor in Japanese men*[1]

| | | Quartile | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 2 | | 3 | | 4 (high) | | |
| | *n* | 1 (low) | OR[2] | 95%CI | OR | 95%CI | OR | 95%CI | *P* for trend |
| BMI | | | | | | | | | |
| <25 kg/m$^2$ | 1443 | 1.00 | 0.88 | 0.64–1.21 | 0.79 | 0.57–1.10 | 0.49 | 0.34–0.69 | <0.0001 |
| ≥25 kg/m$^2$ | 663 | 1.00 | 0.64 | 0.41–0.99 | 0.58 | 0.38–0.91 | 0.55 | 0.35–0.86 | 0.01 |
| Parental history of diabetes | | | | | | | | | |
| No | 1917 | 1.00 | 0.83 | 0.63–1.09 | 0.77 | 0.58–1.01 | 0.50 | 0.37–0.68 | <0.0001 |
| Yes | 189 | 1.00 | 0.45 | 0.17–1.21 | 0.26 | 0.01–0.70 | 0.37 | 0.14–0.93 | 0.06 |
| Smoking | | | | | | | | | |
| No | 1113 | 1.00 | 0.87 | 0.61–1.26 | 0.57 | 0.39–0.84 | 0.50 | 0.34–0.74 | <0.0001 |
| Yes | 993 | 1.00 | 0.68 | 0.46–1.00 | 0.89 | 0.61–1.29 | 0.50 | 0.34–0.76 | 0.004 |
| Leisure-time physical activity | | | | | | | | | |
| <20 MET-h/wk | 1236 | 1.00 | 0.84 | 0.60–1.17 | 0.73 | 0.51–1.03 | 0.47 | 0.32–0.67 | <0.0001 |
| ≥20 MET-h/wk | 870 | 1.00 | 0.70 | 0.46–1.07 | 0.66 | 0.44–1.00 | 0.56 | 0.36–0.87 | 0.01 |

[1] Including impaired fasting plasma glucose, impaired glucose tolerance, and type 2 diabetes.
[2] OR adjusted for hospital, age, occupational rank, parental history of diabetes, BMI, smoking, and leisure-time physical activity.

validation of total energy and nutrient intakes from the present questionnaire have yet not been completed. Men with a high score on a dietary pattern likely consumed more energy than those with a low score; high energy intake usually increases the risk of type 2 diabetes, and the lack of adjustment for energy intake may cause a superfluous positive association. However, energy adjustment only strengthens, rather than diminishes the inverse association between DSFA dietary pattern and glucose tolerance abnormalities, the major finding of the present study. However, we cannot exclude the possibility that the positive trend association between the Japanese dietary pattern and impaired glucose tolerance was a result of confounding by energy intake.

Limitations of factor analysis arise from arbitrary decisions (7,8) involved in selecting and grouping foods for analysis from the questionnaire, in determining the number of factors to retain, in choosing the method of rotation of the initial factors to increase the interpretability of dietary patterns, and in labeling dietary patterns according to their factor loadings. Using factor analysis, Masaki et al. (22) identified a Western breakfast dietary pattern (similar to the DFSA pattern) and an animal dietary pattern in a cohort of men in Tokyo. Kim et al. (23) identified 3 major dietary patterns in a nationwide cohort in Japan: a healthy dietary pattern (similar to the DFSA pattern), a traditional dietary pattern (similar to the Japanese pattern), and a Western dietary pattern (similar to the animal food pattern). These findings suggest the existence of dietary patterns common to the Japanese. However, we also found important differences in loading patterns among these studies. For example, soybean products and seaweeds, which were the most closely correlated with the Japanese dietary pattern in our study, had the highest loadings with a healthy dietary pattern (similar to the DFSA pattern) in another study (23). Therefore, further exploratory studies are required to clarify dietary patterns among the Japanese before this approach is used.

The inverse association between the DFSA pattern and glucose tolerance abnormalities may represent beneficial effects of each food or nutrient contributing to the dietary pattern on glucose metabolism. Results of prospective studies (24–27) suggested that the intake of fruits and/or vegetables is inversely related to the risk of developing type 2 diabetes. Substancesrich in fruits and vegetables that were linked to a decreased risk of diabetes or insulin resistance include fiber (28), carotenoids (29), and magnesium (30). Milk consumption was strongly associated with a decreased risk of developing obesity and the insulin resistance syndrome (31), which are key risk factors for type 2 diabetes. Calcium reduces insulin resistance (32), but other substances in milk may also play a role. In addition to independent effects, there may be complex interactions among food factors constituting the DFSA dietary pattern. Note that the DFSA pattern is similar to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern (33) in that both are rich in fruits, vegetables, and dairy products, and that the DASH diet not only reduces blood pressure (33) but also improves insulin metabolism (34).

Both shochu and beer, 2 major alcohol beverages consumed by the study population, were inversely associated with the DFSA dietary pattern (**Appendix 2**), and men with the lowest quartile of the DFSA pattern score consumed considerably large amounts of alcohol (Table 2). Heavy drinking has been consistently related to increased diabetes risk, whereas moderate drinking may decrease the risk (35). The clear inverse gradient in alcohol consumption may thus account for the decreased odds of glucose tolerance abnormality among men with a higher score for the DFSA dietary pattern.

Confectionaries and soft drinks, which were positively related to the DFSA dietary pattern, may worsen the glucose metabolism due to the potentially detrimental effect of diets high in simple sugars on insulin sensitivity (36). However, epidemiologic evidence is conflicting (37,38). Furthermore, the effect of sugars on glycemic response is greatly attenuated when individuals consume >100 g of carbohydrates (39), as is the case for most Japanese (13) who eat rice as their staple food. Therefore, confectionaries and soft drinks may not play a large role in glucose metabolism in the study subjects. It would also be worth noting that not all food items associated with the DFSA pattern are necessarily causally related to outcome.

The Japanese dietary pattern was characterized by high consumption of traditional Japanese foods (soybean products, seaweeds, pickles, fish, and green tea) and vegetables. Because phytoestrogens in soy protein (40), polyphenols in green tea (41), and (n-3) PUFA rich in fish (42) are suggested to improve

glucose metabolism, the Japanese dietary pattern may likely decrease the risk of type 2 diabetes. However, we found no such association; conversely, the Japanese dietary pattern showed a significant, positive association with impaired glucose tolerance. We have no ready reason for this outcome, but some nutritional characteristics of the Japanese diet (for instance, high in refined carbohydrate but low in protein) may adversely affect glucose metabolism beyond the aforementioned beneficial effects of Japanese foods.

Components of the animal food dietary pattern included meats and marine animal foods except fish. Higher scores of this pattern likely accompany greater consumption of fat, especially saturated fat, which may increase the risk of diabetes (42). Western studies (11,12) suggested that the Western dietary pattern, characterized by frequent red meat intake, confers a risk of type 2 diabetes. In the present study, however, the animal food dietary pattern was not apparently associated with an abnormality in glucose tolerance. The lack of an association may reflect moderate consumption of meat in the Japanese population; mean daily intake in men aged 40–49 y is ~100 g for total meat (13). In the subjects in this study, the mean weekly frequency of consumption was only 1.8 and 1.0 for red and processed meat, respectively (Appendix 2).

In conclusion, the present results indicate that a dietary pattern characterized by frequent consumption of dairy products, confectionaries, fruits, and vegetables but a low intake of local alcoholic beverages may be associated with a reduced risk of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes in Japanese men. Although our finding must be confirmed by prospective studies including women and individuals with various occupational backgrounds, an intervention to change dietary patterns may decrease type 2 diabetes risk in the Japanese population, whose consumption of dairy foods and fruits is currently low (43).

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## APPENDIX 1

*List of the combined food items*

| Food item | Foods or food groups combined |
|---|---|
| Seafood, except fish | Cuttlefish/octopus, shrimp/crab, oyster/shellfish |
| Soybean products | Miso soup, tofu, natto (fermented soybeans) |
| Pickles | Pickled ume, pickled scallion, pickled vegetables |
| Raw vegetables | Tomato, cucumber, cabbage, lettuce, Chinese radish/turnip, onion |
| Vegetable juice | Tomato juice, other juice |
| Heated vegetables | Carrot, pumpkin, onion, green pepper, spinach, leek |
| Seaweeds | Wakame, hijiki/konbu |
| Canned/dried fruits | Canned fruits, dried fruits |
| Fermented dairy products | Yogurt, cheese |
| Confectionary | Chocolate, caramel/candy, cake, Japanese cake, sweetened bun |
| Fried foods | Tempura/other deep-fried foods, fried foods |
| Broiled fish/broiled meat, all kinds | Broiled fish, broiled red meat, broiled chicken |

## APPENDIX 2

*Intakes of selected dietary items according to quartile of dietary pattern score among Japanese men*[1]

| Dietary item | All subjects | DFSA dietary pattern | | | Animal food dietary pattern | | | Japanese dietary pattern | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 (low) | 2, 3 | 4 (high) | 1 (low) | 2, 3 | 4 (high) | 1 (low) | 2, 3 | 4 (high) |
| | | | | | *n/wk* | | | | | |
| Red meat | 1.8 ± 1.4 | 1.9 ± 1.5 | 1.7 ± 1.3 | 1.9 ± 1.6 | 0.7 ± 0.6 | 1.8 ± 1.1 | 3.0 ± 1.5 | 1.9 ± 1.5 | 1.8 ± 1.3 | 1.7 ± 1.4 |
| Processed meat | 1.0 ± 1.2 | 0.8 ± 1.0 | 1.0 ± 1.2 | 1.3 ± 1.4 | 0.5 ± 0.6 | 0.9 ± 1.0 | 1.8 ± 1.6 | 1.1 ± 1.3 | 1.0 ± 1.1 | 1.0 ± 1.3 |
| Poultry | 1.5 ± 1.2 | 1.6 ± 1.4 | 1.5 ± 1.2 | 1.5 ± 1.2 | 0.7 ± 0.5 | 1.4 ± 1.0 | 2.6 ± 1.3 | 1.4 ± 1.1 | 1.5 ± 1.2 | 1.7 ± 1.4 |
| Fish | 3.2 ± 1.9 | 3.5 ± 2.4 | 3.1 ± 1.8 | 3.2 ± 1.8 | 2.5 ± 1.7 | 3.2 ± 1.8 | 3.9 ± 2.1 | 2.3 ± 1.3 | 3.1 ± 1.8 | 4.2 ± 2.3 |
| Seafood, except fish (3)[2] | 2.3 ± 2.2 | 2.0 ± 2.0 | 2.2 ± 2.0 | 2.8 ± 2.5 | 1.3 ± 1.2 | 2.1 ± 1.7 | 3.8 ± 2.8 | 1.8 ± 1.5 | 2.4 ± 2.2 | 2.8 ± 2.4 |
| Egg | 3.4 ± 2.6 | 3.3 ± 2.4 | 3.3 ± 2.7 | 3.6 ± 2.6 | 2.3 ± 2.2 | 3.4 ± 2.3 | 4.5 ± 2.9 | 2.7 ± 2.2 | 3.3 ± 2.4 | 4.1 ± 3.0 |
| Milk | 3.8 ± 3.6 | 2.2 ± 2.3 | 3.6 ± 3.3 | 5.6 ± 4.4 | 3.7 ± 3.9 | 3.7 ± 3.6 | 3.9 ± 3.2 | 3.2 ± 3.4 | 3.8 ± 3.5 | 4.3 ± 3.9 |
| Fermented dairy products (2)[2] | 2.2 ± 2.7 | 0.8 ± 1.0 | 1.8 ± 1.9 | 4.3 ± 3.9 | 2.3 ± 3.4 | 2.1 ± 2.5 | 2.3 ± 2.4 | 2.0 ± 2.8 | 2.0 ± 2.3 | 2.8 ± 3.3 |
| Fruits, not canned/dried | 2.7 ± 2.6 | 1.4 ± 1.6 | 2.6 ± 2.2 | 4.4 ± 3.3 | 2.5 ± 2.8 | 2.8 ± 2.6 | 2.9 ± 2.5 | 2.1 ± 2.2 | 2.7 ± 2.5 | 3.5 ± 3.0 |
| Raw vegetables (6)[2] | 14.6 ± 9.4 | 10.8 ± 6.4 | 13.8 ± 7.7 | 20.0 ± 12.1 | 13.2 ± 10.0 | 14.2 ± 9.5 | 16.6 ± 8.1 | 9.6 ± 6.0 | 13.7 ± 6.9 | 21.4 ± 12.2 |
| Cooked vegetables (6)[2] | 10.0 ± 7.2 | 7.4 ± 5.7 | 9.7 ± 6.5 | 13.1 ± 8.7 | 8.2 ± 7.3 | 9.6 ± 7.2 | 12.4 ± 6.7 | 5.8 ± 3.9 | 9.0 ± 5.5 | 16.0 ± 8.8 |
| Seaweeds (2)[2] | 3.7 ± 3.2 | 2.8 ± 2.6 | 3.6 ± 3.2 | 4.7 ± 3.4 | 3.4 ± 3.4 | 3.5 ± 3.0 | 4.4 ± 3.2 | 1.8 ± 1.5 | 3.4 ± 2.6 | 6.2 ± 3.8 |
| Soybean products (3)[2] | 13.6 ± 7.2 | 13.4 ± 6.8 | 13.2 ± 6.9 | 14.7 ± 8.0 | 13.8 ± 8.0 | 13.2 ± 6.7 | 14.4 ± 7.1 | 8.4 ± 4.5 | 13.2 ± 5.1 | 19.7 ± 8.4 |
| Pickles (3)[2] | 8.2 ± 6.0 | 7.4 ± 5.9 | 7.8 ± 5.4 | 9.6 ± 6.8 | 7.9 ± 6.8 | 8.0 ± 5.8 | 8.8 ± 5.4 | 4.7 ± 3.5 | 7.8 ± 4.9 | 12.3 ± 7.3 |
| Rice[3] | 3.0 ± 1.0 | 3.1 ± 1.0 | 3.0 ± 1.0 | 2.8 ± 1.0 | 3.1 ± 1.0 | 2.9 ± 1.0 | 3.0 ± 1.0 | 2.6 ± 1.0 | 3.0 ± 0.9 | 3.2 ± 0.9 |
| Bread | 1.5 ± 2.2 | 0.5 ± 0.8 | 1.3 ± 1.8 | 3.0 ± 2.9 | 1.4 ± 2.3 | 1.6 ± 2.1 | 1.6 ± 2.2 | 3.0 ± 3.0 | 1.2 ± 1.6 | 0.8 ± 1.4 |
| Confectionary (5)[2] | 2.6 ± 3.2 | 0.9 ± 1.2 | 2.3 ± 2.3 | 5.1 ± 4.4 | 1.9 ± 2.7 | 2.6 ± 3.0 | 3.4 ± 3.7 | 3.1 ± 3.4 | 2.5 ± 3.1 | 2.4 ± 3.1 |
| Green tea[4] | 3.3 ± 2.4 | 3.6 ± 2.5 | 3.3 ± 2.3 | 3.3 ± 2.4 | 3.8 ± 2.5 | 3.3 ± 2.4 | 3.0 ± 2.2 | 2.0 ± 1.7 | 3.3 ± 2.1 | 4.8 ± 2.7 |
| Shochu | 3.0 ± 2.9 | 4.7 ± 2.7 | 2.8 ± 2.8 | 1.5 ± 2.3 | 2.3 ± 2.8 | 3.0 ± 2.9 | 3.5 ± 2.9 | 1.8 ± 2.6 | 3.2 ± 2.9 | 3.7 ± 2.9 |
| Beer | 3.0 ± 2.8 | 3.9 ± 2.8 | 2.9 ± 2.7 | 2.4 ± 2.6 | 1.7 ± 2.3 | 3.2 ± 2.7 | 3.9 ± 2.7 | 2.8 ± 2.8 | 3.2 ± 2.8 | 3.0 ± 2.8 |

[1] Values are means ± SD.
[2] Combined food items (number of foods or food groups combined).
[3] Bowls/d.
[4] Cups/d.

Review

# Statins: Beneficial or Adverse for Glucose Metabolism

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Large-scale clinical trials have established that statin use for lowering blood cholesterol is beneficial in reducing atherosclerotic cardiovascular diseases in different populations. However, the general reputation of statins seems to be clouded by a potential adverse effect of a class of statins on glucose metabolism. This paper reviewed clinical data of statins regarding the effects on diabetes mellitus and glucose metabolism. At least five randomized controlled studies, primarily investigating the protective effect of statins on the risk of cardiovascular diseases, have addressed the effect of statins on glucose metabolism in Western countries. One study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. In Japan, a few case reports have noted a potential adverse effect of atorvastatin on glycemic control in patients with diabetes mellitus; however, seven clinical trials have showed no such effect of atorvastatin although these studies were relatively small in size and short in follow-up. Only one of the two observational studies suggested a possible adverse effect of atorvastatin on glycemic control. Evidence is extremely limited regarding atorvastatin use and deterioration in glycemic control, and further studies are needed to draw a conclusion on this issue.

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**Key words;** Pravastatin, Atorvastatin, Diabetes mellitus, Insulin, Blood glucose

## Introduction

Statins, HMG-CoA reductase inhibitors, enhance the expression of low-density lipoprotein (LDL) receptors in the liver and consequently lower blood LDL cholesterol levels through inhibiting cholesterol synthesis in the liver[1]. From large-scale clinical trials in different populations[2-4], it has been established that statin use substantially reduces the risk of cardiovascular diseases. In addition to lowering LDL cholesterol levels, statins are known to suppress the progression of atherosclerosis by their pleiotropic effects including the improvement of thrombus formation, antioxidant effect, improvement of vascular endothelial cell damage, anti-inflammatory action, and stabilization of plaques[5]. Evidence from clinical trials has given statins the general reputation as very effective and safe cholesterol-lowering drugs, although adverse effects of statins, such as elevation of liver enzymes and rhabdomyolysis, are recognized. However, an incident of fatal rhabdomyolysis associated with cerivastatin raised a concern that the clinical efficacy and safety of statins may differ by the class of statins[6]. Differences in the structural and physical properties of statins might result in the variation in pharmacokinetics, pleiotropic effects, and drug interactions[5].

It has been a matter of recent concern whether atorvastatin deteriorates diabetes mellitus or glycemic control. In 2003, immediately after the introduction of atorvastatin, two independent groups each reported two cases of diabetes mellitus showing deterioration in

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**Table 1.** Atorvastatin use and deterioration of blood glucose status in patients with diabetes mellitus: case reports presented at recent meetings in Japan

| Authors | Main findings | Reference |
|---|---|---|
| Nunoi, et al. | Deteriorated HbA1c with ATR for 2 months (2 cases). | J Jpn Diab Soc, 46: 202, 2003 |
| Murakami, et al. | Deteriorated FBS with ATR 5 mg for 3 M and 10 mg for 2 months (2 cases). | J Cardiol, 42 (Suppl 1): S455, 2003 |
| Katoh, et al. | Deteriorated HbA1c with ATR 5 mg for 1 month and with ATR 10 mg for 4 months (2 cases). | J Jpn Diab Soc, 48: 71, 2005 |
| Kodera, et al. | Deteriorated non-fasting BS/HbA1c with ATR for 3-4 months (2 cases) | J Jpn Diab Soc, 48: 392, 2005 |
| Seguchi, et al. | Deteriorated FBS/HbA1c with ATR for 3-6 months (3 cases) | J Jpn Diab Soc, 48: 392, 2005 |
| Fukuniwa, et al. | Deteriorated HbA1c with ATR 5 mg for 2 months and then with PRV 10 mg for 2 months (1 case) | J Jpn Diab Soc, 48: 451, 2005 |

ATR: atorvastatin, BS: blood sugar, FBS: fasting blood sugar, PRV: pravastatin.
Based on the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, proceedings, and human).

glycemic control during treatment with atorvastatin, and at least eight such cases were reported subsequently at meetings in Japan (**Table 1**). Very recently, a case of type 2 diabetes mellitus occurring after atorvastatin treatment was published[7]. In this case, however, hyperglycemia, which was resolved with insulin therapy and discontinuation of atorvastatin, recurred with pravastatin use. As discussed in detail below, a substudy of a multicenter randomized controlled trial, which was presented at the 2004 meeting of the American Heart Association (AHA), suggested that a high dose of atorvastatin (80 mg/day) might deteriorate glycemic control[8]. In this paper, we review clinical data concerning the effects of statins on glucose metabolism, especially from the safety aspect, and discuss the possible mechanisms of these effects. For this task, we searched for relevant articles in PubMed with the combination of "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[MeSH], "Clinical Trials"[MeSH] and "Diabetes Mellitus"[MeSH], and also the Japan Medical Abstracts Society web version 3 with a combination of key words (HMG-CoA reductase inhibitors, diabetes mellitus, original article/proceedings, and human). The search was limited to publications in the year 2000 and thereafter, and was done on January 10, 2006. Related articles were also searched for by scanning the references quoted in the articles at hand.

## Randomized Controlled Trials in Western Countries

The effects of statins on the risk of diabetes mellitus or glycemic control have been directly addressed in at least five randomized controlled trials with the event of cardiovascular diseases as the primary endpoint. The West of Scotland Coronary Prevention Study[9] was the first clinical trial which investigated the risk of diabetes mellitus associated with statin treatment. Originally, it was a double-blind trial in which 6,595 men aged 45-64 years with hypercholesterolemia but no evidence of cardiovascular disease were randomized to receive either pravastatin (40 mg/day) or placebo treatment[3]. The subjects in the substudy were 5,974 men who had two or more post-randomization measurements of blood glucose and had neither self-reported diabetes nor fasting blood glucose of ≥ 7.0 mmol/L at baseline. The incidence of diabetes mellitus was defined as two glucose measurements of ≥ 7.0 mmol/L and at least one measurement of ≥ 2.0 mmol/L above the baseline level or newly started prescription of hypoglycemic drugs. During the follow-up period of 3.5-6.1 years, 139 became diabetic. After adjustment for body mass index, triglyceride, blood glucose, and other characteristics at baseline, the patients assigned to pravastatin therapy had a hazard ratio of 0.70 (95% confidence interval, 0.50-0.98) for transition to diabetes mellitus[9].

In the MRC/BHF Heart Protection Study[10], 20,536 subjects aged 40 to 80 years with and without diabetes mellitus were randomized to receive either simvastatin (40 mg/day) or placebo. The mean duration of follow-up was 4.8 years for participants with diabetes mellitus at entry and 5.0 years for those without. Among the 14,573 subjects without known diabetes mellitus at baseline, there was no difference in the incidence of diabetes mellitus defined as the initiation of oral hypoglycemic or insulin treatment or a specific report of new diabetes mellitus (4.6% in the simvastatin group and 4.0% in the placebo group, $p=0.10$)[11]. Furthermore, among a random sample of 1,087 patients with diabetes mellitus at baseline, HbA1c levels slightly increased in both simvastatin (0.15%) and placebo (0.12%) groups during the study period, with no measurable difference between the

two ($p=0.8$)[11].

In the Anglo-Scandinavian Cardiac Outcomes Trial[12], 19,342 hypertensive patients aged 40 to 79 years were randomized to either of two antihypertensive regimens and 10,305 with non-fasting total cholesterol concentrations of 6.5 mmol/L or less were further randomized to either atorvastatin (10 mg/day) or placebo treatment. The median follow-up was 3.3 years. The occurrence of diabetes mellitus was prespecified as a tertiary endpoint. There was no difference in the development of diabetes mellitus between the atorvastatin and placebo treatments; the hazard ratio for atorvastatin versus placebo was 1.15 (95% confidence interval, 0.91 to 1.44).

In a substudy of the Pravastatin or Atorvastatin Evaluation in Myocardial Infarction (PROVE-IT) presented at the 2004 AHA meeting[8], the effects of the two statins on glycemic control were evaluated. PROVE-IT was the first large-scale clinical study comparing two statins[13]. In this study, 4,162 patients were randomized to receive intensive lipid-lowering therapy with atorvastatin (80 mg/day) or standard lipid-lowering therapy with pravastatin (40 mg/day) immediately after the occurrence of acute coronary syndrome. As compared with patients treated with pravastatin, those with atorvastain had a higher risk of developing HbA1c>6.0% among those with baseline HbA1c ≤ 6.0% regardless of diabetes mellitus; the pooled hazard ratio was estimated to be 1.84 (95% confidence interval 1.52-2.22). This finding does not necessarily indicate that atorvastatin increases the risk of deterioration in glycemic control because the comparison was made against pravastatin treatment.

The Collaborative Atorvastatin Diabetes Study investigated the protective effect of atorvastatin (10 mg/day) versus placebo specifically on cardiovascular disease in 2,838 patients with type 2 diabetes mellitus[14]. No difference was noted between the two regimens with respect to changes in HbA1c levels and the therapeutic modality for diabetes mellitus. The mean HbA1c levels at the baseline were 7.9% in the atorvastatin group and 7.8% in the placebo group. The corresponding values after 4 years of follow-up were 8.3% and 8.1%, respectively. At the baseline, insulin was used in 19.7% of patients in the atorvastatin group and 18.9% of patients in the placebo group. These proportions had not changed significantly at the end of the follow-up period (atorvastatin 20.5% and placebo 18.2%).

In summary, one study showed that pravastatin (40 mg/day) was protective against the development of diabetes mellitus. Two studies of atorvastatin (10 mg/day) and one study of simvastatin (40 mg/day) showed no measurable effect of these regimens on the risk of diabetes mellitus or the clinical course of diabetes mellitus. One study of atorvastatin (80 mg/day) versus pravastatin (40 mg/day) suggested a deterioration of glucose metabolism associated with a high dose of atorvastatin. It should be noted that the onset or deterioration of diabetes mellitus was defined differently in the studies, however.

## Clinical Trials and Observational Studies in Japan

None of the reported clinical trials regarding statins and cardiovascular diseases has been extended to examine the effects of statins on the risk of diabetes mellitus or glucose metabolism[4, 15]. With hindsight, a possible adverse effect of atorvastatin on glucose metabolism was noted in a long-term one-arm trial of 287 patients with total cholesterol of ≥ 220 mg/dL. The primary purpose of this trial was to investigate the efficacy of atorvastatin 5-10 mg/day on serum lipids[16]. The majority (81%) of the patients received atorvastatin 10 mg/day throughout the study period. The prescribed dose was changed from 10 mg/day to 20 mg/day in 7% of the patients, from 10 mg/day to 5 mg/day in 5%, and from 5 mg/day to 10 mg/day in 4%. The episode of a pre-specified abnormal elevation of fasting blood glucose was fairly frequently observed during the one-year period, as shown in **Table 2**. Furthermore, the grade of abnormal elevation was more severe for blood glucose than for other laboratory measurements. Sixteen laboratory tests were evaluated in terms of severity. The majority (82%) of the episodes of abnormal change in laboratory tests other than glucose were classified as grade 1 (slight deterioration), but 15 of the 21 episodes of abnormal elevation of blood glucose were classified as grade 2 (moderate deterioration) or grade 3 (severe deterioration). The abnormal elevation of HbA1c was also commonly seen during the study period. It should be noted that the abnormal elevation of blood glucose or HbA1c was evaluated in terms of the number of episodes rather than cumulative incident cases.

We identified 11 published studies examining changes in fasting blood glucose and/or HbA1c after treatment with a specific statin in diabetes patients (**Table 3**). Of these, three were randomized trials[17-19], six were one-arm trials[20-25], and two were retrospective, observational studies[26, 27]. Except for three studies[22, 23, 26], these studies were very small in size with fewer than 100 patients, and a relatively short follow-up period. None of the seven trials found any measurable adverse effect of atorvastatin on glycemic con-

**Table 2.** Episodes of abnormal laboratory tests occurring in hypercholesterolemic patients treated with atorvastatin 5-20 mg/day for one year

| Abnormal laboratory test | No. of patients | No. of episodes |
|---|---|---|
| Elevation of gamma-glutamyltransferase | 287 | 50 (17.4%) |
| Elevation of alanine aminotrasferase | 287 | 34 (11.8%) |
| Elevation of aspartate aminotrasferase | 287 | 26 (9.1%) |
| Elevation of fasting blood glucose | 281 | 21 (7.5%) |
| Decreased testosterone | 274 | 20 (7.3%) |
| Elevation of creatinine phosphokinase | 287 | 19 (6.6%) |
| Elevation of choline esterase | 287 | 16 (5.6%) |
| Elevation of HbA1c | 282 | 15 (5.3%) |

Derived from reference (15)

**Table 3.** Clinical trials and observational studies concerning statins and glycemic control in patients with diabetes mellitus in Japan

| Authors (ref.) | Type of study | No. of patients | Statin | Dose (mg/day) | Period | Main findings |
|---|---|---|---|---|---|---|
| Tanaka, et al.[17] | RCT | 40 | Atorvastatin<br>Placebo | 10<br>– | 12 weeks | No change in HbA1c for each group. |
| Endo, et al.[18] | RCT | 47 | Atorvastatin<br>Pravastatin | 10<br>20 | 4 months | No change in HbA1c for each statin. |
| Kameda, et al.[19] | RCT | 14 | Atorvastatin<br>Bezafibrate | 10<br>400 | 9 months | No change in FBS/HbA1c for each drug. |
| Sato and Miyachi[20] | One-arm trial | 26 | Atorvastatin | 10-20 | 8 weeks on average | No change in HbA1c. |
| Hamano[21] | One-arm trial | 35 | Atorvastatin | 10 | 12 months | No change in FBS/HbA1c. |
| Sasamoto[22] | One-arm trial | 180 | Atorvastatin | 5-40 | 3-15 months | No change in FBS/HbA1c. |
| Suzuki[23] | One-arm trial | 160 | Atorvastatin | 10 | 3 months to 3 years | No change in HbA1c |
| Yamada, et al.[24] | One-arm trial | 27 | Pitavastatin | 2 | 8 weeks | HbA1c increased by 0.17% (95% CI 0.01, 0.33). |
| Yamada[25] | One-arm trial | 57 | Pitavastatin | 1-2 | 30 months on average | No change in FBS |
| Seino, et al.[26] | Observational study | 809 | Pravastatin<br>Simvastatin<br>Fluvastatin<br>Atorvastatin | 5-20<br>2.5-10<br>20-60<br>5-10 | 3.9 years<br>3.4<br>1.9<br>0.9 | No change in FBS/HbA1c for each statin. |
| Osaki, et al.[27] | Observational study | 67 | Atorvastatin<br>Pravastatin | 10<br>10 | 2-3 months | Deteriorated HbA1c (≥ 10% relatively) was more frequent for atorvastatin (7/25, 28%) than pravastatin (3/42, 7%). |

RCT: randomized controlled trial, FBS: fasting blood sugar.

trol[17-23]. Only one observational study reported that deterioration of HbA1c was statistically significantly more frequent for atorvastatin than pravastatin[27], whereas the other observational study found no measurable change in fasting blood glucose or HbA1c in relation to atorvastatin and other statins[26]. On the other hand, one of the two studies concerning pitavastatin showed a statistically significant increase in HbA1c after 8-week treatment[24]. Findings from case reports may often signal an alarming adverse effect of a newly introduced drug, but they may sometimes be an extreme of random variation. One study graphically presented HbA1c values of 26 subjects before and after atorvastatin treatment[20]. HbA1c increased markedly in a few individuals, and also decreased substantially in an almost equal number of subjects. Amelioration may not have been taken as seriously as deterioration in the routine clinical practice.

In summary, although the case reports suggested a potential adverse effect of atorvastatin in patients

with diabetes mellitus, none of the seven clinical trials provided supporting evidence. Only one of the two observational studies reported a more frequent deterioration of HbA1c in treatment with atorvastatin than with pravastatin. Observational findings in clinical practice require caution in their interpretation because they may have been ascribed to other concurrent factors associated with the deterioration of diabetes mellitus. Thus, evidence showing that atorvastatin at a dose commonly used in Japan deteriorates glycemic control in patients with diabetes mellitus is extremely limited.

## Mechanisms of the Effects of Statins on Glucose Metabolism

Evidence is very limited as regards the mechanisms by which statins exert any influence on glucose metabolism. Statins may improve insulin resistance and be protective against glucose intolerance through their anti-inflammatory effects[28, 29]. Inflammatory markers have been related to an increased risk of diabetes mellitus in adults[30, 31], and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-$\alpha$ are implicated as being linked with insulin resistance through their influence on insulin receptor[32, 33]. On the other hand, statins can deteriorate glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone ($CoQ_{10}$), which are normally produced during the process of cholesterol synthesis from acetyl CoA via mevalonic acid. Isoprenoid is known to enhance glucose uptake by upregulating the membrane transporter protein glucose transporter 4 (Glut 4), which plays a role in glucose uptake in adipocytes[34]. Suppressed biosynthesis of ubiquinone ($CoQ_{10}$), an essential factor in the electron-transfer system in mitochondria, may result in delayed ATP production in pancreatic $\beta$ cells and thereby impair insulin release. It was recently shown that atorvastatin treatment resulted in a reduction of serum $CoQ_{10}$ levels, which was positively correlated with LDL cholesterol levels[35].

These mechanisms may differ by the property of statins. Water-soluble statins, such as pravastatin, are hepatocyte-specific and are not readily taken up by pancreatic cells and adipocytes. Lipid-soluble statins, such as simvastatin and atorvastatin, enter extrahepatic cells easily and may inhibit isoprenoid protein synthesis, consequently attenuating insulin action. Lovastatin, a lipid-soluble statin, was shown to down-regulate insulin-responsive Glut 4 and up-regulate Glut 1 in 3T3-L1 adipocytes leading to marked inhibition of insulin-stimulated glucose transport[34]. Another lipid-soluble statin, simvastatin, inhibited glucose-induced increase in intracellular $Ca^{2+}$ of pancreatic $\beta$ cells, leading to the inhibition of insulin secretion in a dose-dependent manner, while water-soluble pravastatin had absolutely no effect even at a high concentration of 100 $\mu$g/mL[36]. The inhibitory potency of HMG-CoA reductase and lipophilicity of statins may be related to different effects on glucose metabolism, although further studies are needed.

## Conclusion

A few clinical studies have suggested that atorvastatin, especially at a high dose, may deteriorate glucose metabolism while pravastatin might improve glucose metabolism; however, evidence is extremely limited, and further studies are needed to draw a conclusion on this issue. The mechanisms by which these statins affect glucose metabolism also need to be studied further. The effect of statins on glucose metabolism, if any, seems particularly important in Japan. Japanese are more prone to developing diabetes mellitus than Caucasians[37], and coronary risk is lower in Japan as compared with Western countries. A decreased risk of coronary artery disease conferred by statins well surpasses any adverse effect of intensive statin therapy in Western countries; however, it is uncertain whether such intensive statin therapy is also applicable in Japan.

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# Gender Difference in Coronary Events in Relation to Risk Factors in Japanese Hypercholesterolemic Patients Treated With Low-Dose Simvastatin

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**Background** Gender differences between the risk factors for coronary heart disease and coronary events were examined in the Japan Lipid Intervention Trial, a 6-year observational study.

**Methods and Results** Men (12,575) and women (27,013) were analyzed for risk of coronary events (acute myocardial infarction and sudden cardiac death). Simvastatin reduced serum low-density lipoprotein cholesterol (LDL-C) by 27% in both genders, and increased serum high-density lipoprotein cholesterol (HDL-C) in men (5%) and women (4%). The incidence of coronary events was lower in women (0.64/1,000 patient-years) than in men (1.57/1,000 patient-years). The risk of coronary events increased by 18% in men and 21% in women with each 10 mg/dl elevation of LDL-C, and decreased by 39% in men and 33% in women with each 10 mg/dl elevation of HDL-C. The risk increased proportionally with aging in women, but not in men. Diabetes mellitus (DM) was more strongly related to the risk of coronary events for women (relative risk 3.07) than for men (relative risk 1.58).

**Conclusions** The incidence of coronary events is lower in women. Serum LDL-C is related to an increased risk of coronary events to the same extent in both genders. DM seems to be a more important risk factor in women, trading off the lower risk of coronary events among them. (*Circ J* 2006; **70:** 810–814)

**Key Words:** Coronary events; Hyperlipidemia; Risk factors; Serum cholesterol; Sex differences

Coronary heart disease (CHD), including myocardial infarction and cardiac sudden death, is one of the leading causes of death in Japan.[1] The risk of developing CHD is known to be markedly different between men and women:[2,3] CHD incidence is 2 to 5 times higher among middle-aged men than women. In the Japan Lipid Intervention Trial (J-LIT);[4–7] we previously reported that serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations were positively and serum high-density lipoprotein cholesterol (HDL-C) concentration was inversely related to CHD or cerebrovascular disease risk in patients under treatment for hypercholesterolemia. The role of coronary risk factors in the development of CHD has been studied extensively in men;[8–10] but relatively few studies have investigated women.[2,11]

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This study aimed to assess gender differences in the association of risk factors with CHD in the J-LIT data. The J-LIT is a nationwide cohort study of 52,421 hypercholesterolemic patients treated with open-labeled low-dose simvastatin (5–10 mg/day).[4,5] The J-LIT included a large number of female patients, and we were able to investigate the gender difference in the role of risk factors in the occurrence of coronary events.

## Methods

*Study Design*

The design of the J-LIT study has been previously described.[12] Briefly, study patients with serum TC concentration ≥220 mg/dl, men aged 35–70 years and postmenopausal women aged 70 years or less, were treated with 5–10 mg/day of simvastatin. Body weight, serum lipid concentrations (TC, LDL-C, HDL-C, and triglyceride (TG)) were measured at baseline, and patients were interviewed as regards family history of CHD, number of cigarettes smoked, and the amount of alcohol ingestion. Serum lipid concentrations and CHD-related events (acute myocardial infarction and cardiac sudden death) were monitored every 6 months for 6 years in all patients, including those who discontinued simvastatin. Serum lipid concentrations were determined in each study institution, and the serum LDL-C concentration was calculated using the Friedewald formula for patients with TG concentration ≤400 mg/dl.[13] Study physicians recommended dietary and exercise-therapy for hyperlipidemia to all patients. Additional lipid-lowering

agents were allowed only when an adequate response in serum TC concentration was not gained by simvastatin monotherapy. Each patient was informed of the purpose and method of the study, drug efficacy and the need for long-term treatment and they gave verbal, not written, informed consent.

*Subjects*

Patients who had been previously treated with a lipid-lowering agent were screened for eligibility after a washout period of at least 4 weeks. For patients previously treated with probucol, the washout period was at least 12 weeks. The exclusion criteria were the occurrence of acute myocardial infarction or stroke within the past month, concurrent uncontrolled diabetes mellitus (DM), serious hepatic or renal disease, secondary hypercholesterolemia, cancer or any other illness with potentially poor survival.

Of the 52,421 patients enrolled, 5,127 were excluded because of a history of CHD, 4,934 for lack of follow-up data, and 2,772 for missing data of the covariates. Therefore, data from 39,588 patients (12,575 men, 27,013 women) were used in the present study.

*Endpoints*

The primary endpoints were major coronary events, defined as nonfatal and fatal myocardial infarction and sudden cardiac death. Incidence of myocardial infarction or death was counted once for each patient during the treatment, and the follow-up data thereafter were excluded from the analysis. The events were reviewed and determined by the Endpoint Classification Committee.

*Statistical Analysis*

The mean lipid concentrations were calculated using data available at the follow-up points in time during the treatment period. The data of lipid concentrations after the onset of events were excluded. Data during the treatment period after discontinuation of simvastatin were also included for analysis. Mean values for serum lipid concentrations and age were tested with unpaired t-test, and the prevalence of baseline characteristics were tested with the chi-square test for comparison between men and women. Patients in each sex were categorized into 5–6 groups according to the mean lipid concentrations of treatment period for TC, TG, LDL-C and HDL-C with intervals of 20, 50, 20, 10 mg/dl, respectively, and for the LDL-C/HDL-C ratio with an interval of 0.5. The reference category for the relative risk was set on the group with the lowest lipid concentrations and the lowest value of LDL-C/HDL-C ratio. Relative risks and the 95% confidence intervals (CI) were calculated using the Cox proportional hazards model with adjustment for baseline characteristics such as sex, age, hypertension, DM, body mass index (BMI), ECG abnormality, family history of CHD, alcohol ingestion and cigarette smoking. Heterogeneity between men and women was evaluated by the likelihood ratio test. Two-sided p-value <0.05 was considered statistically significant. All the statistical calculations were performed using SAS software (version 8.02, SAS Institute, Inc, Cary, NC, USA).

## Results

*Serum Lipids and Other Risk Factors*

There were no significant difference as regards the prevalence of obesity (BMI ≥25.0 kg/m$^2$), hypertension, ECG abnormality, and family history of CHD between men and women (Table 1). In men, the prevalence of DM was higher ($p<0.001$), and cigarette smoking and alcohol ingestion were much more frequent ($p<0.001$).

**Table 1 Baseline Characteristics of the Subjects**

| | *Men (n=12,575)* | *Women (n=27,013)* |
|---|---|---|
| *Age (years)* | *54.0 (9.1)* | *59.5 (6.5)* |
| *Obesity (%)*[a] | *36.7* | *32.2* |
| *Hypertension (%)*[b] | *45.4* | *46.3* |
| *Diabetes mellitus (%)*[c] | *20.0* | *13.9* |
| *ECG abnormality (%)*[d] | *13.4* | *12.9* |
| *Family history of CHD (%)*[e] | *5.1* | *4.8* |
| *Cigarette smoking (%)*[e] | *43.8* | *4.1* |
| *Alcohol use (%)*[e] | *73.4* | *8.7* |
| *Lipid profiles* | | |
| *Baseline (mg/dl)* | | |
| *TC* | *268 (41)* | *271 (31)* |
| *LDL-C* | *178 (34)* | *184 (33)* |
| *TG* | *250 (241)* | *169 (111)* |
| *HDL-C* | *49 (15)* | *55 (15)* |
| *During the treatment (mg/dl)* | | |
| *TC* | *218 (31)* | *221 (29)* |
| *LDL-C* | *130 (31)* | *135 (28)* |
| *TG* | *198 (133)* | *148 (77)* |
| *HDL-C* | *51 (13)* | *57 (14)* |

*Figs are mean±SD unless otherwise specified.*
*CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol.*
*[a] Body mass index ≥25 kg/m$^2$. [b] Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg or medication for hypertension. [c] Fasting plasma glucose ≥140 mg/dl or medication. [d] Study physician's diagnosis. [e] Self-reported information.*

Lipid profiles at baseline and during the treatment period are shown for men and women in Table 1. Men had higher concentrations of serum TG and lower concentrations of serum HDL-C at baseline and during the treatment in comparison with women. Mean percent changes in the TC, LDL-C, TG, and HDL-C concentrations from baseline to during the treatment in men were −18.8% ($p<0.001$), −27.2% ($p<0.001$), −20.9% ($p<0.001$), and +4.7% ($p<0.001$), respectively, and the corresponding values in women were −18.2% ($p<0.001$), −26.6% ($p<0.001$), −12.8% ($p<0.001$) and +4.4% ($p<0.001$), respectively.

*Incidence of Coronary Events*

The incidence of coronary events was greater (105/12,575) in men than in women (93/27,013) during the treatment period. Incidence rates of coronary events per 1,000 patient-years were 1.57 in men and 0.64 in women. The age-adjusted relative risk of coronary events for men vs women was 2.81 (95% CI 2.10–3.76, $p<0.001$).

*Serum Lipid Concentrations During the Treatment Period and Risk of Coronary Events*

The risk of coronary events in relation to serum lipid concentrations is shown in Table 2. Increased risk for coronary events was evident at TC ≥240 mg/dl and LDL-C ≥160 mg/dl in both men and women. An increased risk of CHD associated with elevated concentration of TG (≥250 mg/dl) was noted in women but not in men. In men, the relationship between TG and CHD risk was not measurable. A lower risk of coronary events associated with elevation in HDL-C was seen in both sexes, but the protec-