Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study1–3

Ehab S Eshak, Hiroyasu Iso, Kazumasa Yamagishi, Yoshihiro Kokubo, Isao Saito, Hiroshi Yatsuya, Norie Sawada, Manami Inoue, and Shoichiro Tsugane

ABSTRACT

Background: Rice consumption has been associated with risk of type 2 diabetes, but its relation with cardiovascular disease (CVD) is limited. Objective: We examined the association between rice consumption and risk of CVD incidence and mortality in a Japanese population. Design: This was a prospective study in 91,223 Japanese men and women aged 40–69 y in whom rice consumption was determined and updated from 3 self-administered food-frequency questionnaires, each 5 y apart. Follow-up for incidence was from 1990 to 2009 in cohort I and 1993 to 2007 in cohort II and for mortality was from 1990 to 2009 in cohort I and 1993 to 2009 in cohort II. HRs and 95% CIs of CVD incidence and mortality were calculated according to quintiles of cumulative average rice consumption. Results: In 15–18 y of follow-up, we ascertained 4395 incident cases of stroke, 1088 incident cases of ischemic heart disease (IHD), and 2705 deaths from CVD. Rice consumption was not associated with risk of incident stroke or IHD; the multivariable HR (95% CI) in the highest compared with lowest rice consumption quintiles was 1.01 (0.90, 1.14) for total stroke and 1.08 (0.84, 1.38) for IHD. Similarly, there was no association between rice consumption and risk of mortality from CVD; the HR (95% CI) for mortality from total CVD was 0.97 (0.84, 1.13). There were no interactions with sex or effect modifications by body mass index for any endpoint. Conclusion: Rice consumption is not associated with risk of CVD morbidity or mortality. Am J Clin Nutr 2014;100:199–207.

INTRODUCTION

White rice is a major staple food of the Japanese people and central to the Japanese diet. Although rice consumption in Japan has decreased over the past several decades, nearly 29% of total caloric intake for the Japanese is still derived from rice (1). Rice consumed by the Japanese is primarily refined white rice and not brown rice. Compared with brown rice, white rice contains less dietary fiber and fewer vitamins and minerals (2), which may be positively associated with greater risk of type 2 diabetes and cardiovascular disease (CVD) (3). However, white rice is free of cholesterol and has a very low sodium content (3), which was the basis for its use in the traditional Kempner rice diet where it was used as an aid to treat hypertension (4). Therefore white rice consumption might also be considered to be inversely associated with risk of CVD. A meta-analysis showed that white rice consumption was associated with elevated risk of type 2 diabetes in Japanese men and women but not in men in the Japan Public Health Centre-based (JPHC) study (6). However, a recent cohort study in Spain showed an inverse association between rice consumption and risk of type 2 diabetes (7). In some (8–13) but not all (14–19) studies, foods rich in refined carbohydrates, such as white rice, have been associated with increased risk of CVD, especially in women. However, few studies have been conducted in Asian populations, who are known to consume large quantities of rice (12, 13, 18, 19). To our knowledge, associations between rice consumption with risk of incident stroke and ischemic heart disease (IHD) have not been previously investigated. A Japanese study suggested a positive association with mortality from stroke in young women with low BMI (12), whereas another Japanese study showed an inverse association with mortality from IHD in elderly men with high BMI (18).

With the use of data from a large-scale, population-based cohort study in Japan, we aimed to examine the prospective association between white rice consumption and risk of stroke and mortality from IHD, and ischemic heart disease (IHD), and 2705 deaths from CVD. Rice consumption was not associated with risk of incident stroke or IHD; the multivariable HR (95% CI) in the highest compared with lowest rice consumption quintiles was 1.01 (0.90, 1.14) for total stroke and 1.08 (0.84, 1.38) for IHD. Similarly, there was no association between rice consumption and risk of mortality from CVD; the HR (95% CI) for mortality from total CVD was 0.97 (0.84, 1.13). There were no interactions with sex or effect modifications by body mass index for any endpoint. Conclusion: Rice consumption is not associated with risk of CVD morbidity or mortality. Am J Clin Nutr 2014;100:199–207.

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2The Japan Public Health Centre-based Prospective Study was supported by Grants-in-Aid for cancer Research (19sh1-2) and a Health Sciences Research Grant [research on Comprehensive Research on Cardiovascular disease (H19-016)] from the Ministry of Health, Labour and Welfare of Japan.
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4Abbreviations used: CVD, cardiovascular disease; FFQ, food-frequency questionnaire; GI, glycemic index; GL, glycemic load; IHD, ischemic heart disease; JACC, Japan Collaborative Cohort; JPHC, Japan Public Health Centre-based; PHC, public health center.

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and IHD incidence and mortality in Japanese men and women both combined and sex specifically. Also, a stratified analysis by BMI (kg/m$^2$) was conducted because overweight and obesity might represent intermediate endpoints or pathways rather than confounders for rice. In addition, this analysis provided the ability to examine previous studies that yielded different results (12, 18) and evaluate the issue of whether overweight and obese subjects may have changed their rice consumption to lose weight because rice is a major source of caloric intake. Because rice was positively associated with risk of type 2 diabetes in our cohort study (6), it was hypothesized that rice consumption may be associated with higher risk of CVD.

**SUBJECTS AND METHODS**

**Study population**

The JPHC study, which is a large, Japanese, Nationwide, prospective cohort study, was launched in 5 public health centers (PHCs) for cohort I and 6 PHCs for cohort II. The study population was defined as all inhabitants in study areas aged 40–59 y in cohort I and 40–69 y in cohort II. The study design has been described in detail previously (20) and was approved by the Institutional Review Board of the National Cancer Centre, Tokyo, Japan.

**Baseline survey**

The baseline was in 1990 for cohort I and 1993 for cohort II; with the use of a self-administered questionnaire, study subjects were asked to provide information regarding personal and familial medical histories, lifestyles, and other health-related information. The dietary habits of subjects were assessed by using a food-frequency questionnaire (FFQ) of 44 items for cohort I (21) and 52 items for cohort II. The response rate for the baseline questionnaire was 77% in men and 83% in women.

**Five- and 10-y follow-up surveys**

We conducted 5-y follow-up, self-administered questionnaire surveys in 1995 for cohort I and 1998 for cohort II and 10-y surveys in 2000 for cohort I and 2003 for cohort II. FFQs used in 5- and 10-y follow-up surveys were developed to estimate dietary intake from 138 food items and was validated for estimations of various nutrients and food groups (22). Data on demographics, lifestyles, personal and familial medical histories, and other health-related information were also obtained. The response rate for the 5-y questionnaire was 72% in men and 79% in women and, for the 10-y questionnaire, was 70% in men and 78% in women.

**Dietary assessment**

Frequencies of consumption were reported for the previous month in baseline FFQs. We used the following 4 response choices in the cohort I FFQ: almost never, 1–2 and 3–4 d/wk, and almost daily. Responses of cohort II’s baseline FFQ were selected from the following 5 choices: never; <1, 1–2, and 3–4 d/wk; and almost daily. Portion sizes for food items were determined on the basis of 14- to 28-d diet-record data. Data on the daily consumption of standard rice bowls (a standard bowl was equal to 140 g), with possible answers as “not even one per day” or “approximately XX bowls per day” in cohort I and “almost not” or “approximately XX bowls per day” in cohort II, were also calculated (21, 23).

In 5- and 10-y follow-up surveys, a standard unit and relative portion sizes for each food item were included and were identical for both cohorts. Frequency-response choices were as follows: never; 1–3 times/mo; 1–2, 3–4, and 5–6 times/wk; or 1, 2–3, 4–6, and ≥7 times/d. Relative portion sizes were as follows: small (50% smaller), medium (same as the standard), and large (50% larger). Participants were asked to determine their consumption of rice on the basis of their usual rice bowl sizes [small (110 g), standard (140 g), and large (170 g)] and the number of bowls consumed daily from 9 options that ranged from <1 to ≥10 bowls/d (23). Daily food intakes were computed by multiplying the frequency by relative portions for each food item in FFQs. Daily intakes of nutrients were calculated by using the food-composition table developed for each FFQ on the basis of the fifth revised edition of the Standard Tables of Food Composition in Japan (24). Caloric-adjusted nutrient consumptions were calculated by using the residual method (25). The validity of rice consumption estimated by the 5-y FFQ was assessed in subsamples by using both 14- and 28-d dietary records. Spearman’s correlation coefficients between intake values for rice derived from the FFQ and those derived from dietary records were 0.67 in men and 0.55 in women. For reproducibility of estimations between 2 FFQs administered 1 y apart, respective Spearman’s correlation coefficients were 0.79 in men and 0.71 in women. The rice consumption from the FFQ (mean ± SD: 439 ± 200 g/d in men and 334 ± 146 g/d in women) did not differ from that for dietary records (480 ± 159 g/d in men and 315 ± 101 g/d in women) (26).

**Inclusion and exclusion criteria**

Participants who lived in 2 PHCs were excluded because of differences in recruitment criteria. Of the remaining 116, 672 subjects, responses were obtained from 95,405 participants [43,149 subjects in cohort I and 52,256 subjects in cohort II (overall response rate 82%; 80% in cohort I and 84% in cohort II)] and were included in the current study. At baseline, participants who did not respond to rice-intake items (n = 528; 98 subjects in cohort I and 430 subjects in cohort II) and participants with implausible energy intakes [outside of the mean ± 3 SD: n = 744 subjects; 334 subjects in cohort I and 410 subjects in cohort II] were excluded. Participants who reported a history of stroke, IHD, or cancer (n = 2910; 1216 subjects in cohort I and 1694 subjects in cohort II) at baseline were also excluded, which left a total of 91,223 participants (41,501 subjects in cohort I and 49,722 subjects in cohort II) and were ultimately included in our analysis.

**Endpoint assessment**

**Morbidity**

A total of 78 major hospitals with the capability of treating patients with IHD and stroke were registered within the administrative districts of JPHC cohorts. Physicians, who were unaware of the patients’ lifestyle data, reviewed medical records at each hospital. Incidences of fatal and nonfatal stroke were...
vascular risk factors and population characteristics were pre-
determined if the criteria of the National Survey of Stroke (27)
were met, specifically, the presence of focal neurologic deficits
of sudden or rapid onset that lasted ≥24 h or until death. For
each subtype of stroke (ie, hemorrhagic and ischemic strokes),
a diagnosis was established on the basis of data collected from
computed tomography scans, magnetic resonance images, or
autopsy.

Fatal IHD events and nonfatal myocardial infarction were
confirmed through medical records according to the criteria of the
Monitoring Trends and Determinants of Cardiovascular Disease
project (28), which requires evidence from electrocardiograms,
cardiac enzymes, or autopsy.

To confirm and verify nonfatal stroke and myocardial in-
farction, for subjects who reported the occurrence of coronary or
stroke events in the 10-y follow-up questionnaire but who were
not registered in the stroke or IHD registry, contact attempts
were made by letter or telephone to obtain permission to review rel-
levant medical records. Of 653 subjects who reported an un-
registered stroke, 582 subjects (89%) were successfully
contacted, and 245 subjects provided information that was
consistent with suspected strokes. Of these 245 subjects, 213
participants (87%) provided written informed consent for their
records to be reviewed by physicians. In these subjects, a di-
agnosis of stroke was verified for 165 subjects, and these cases
were, therefore, included in the registry. Of 288 subjects who
reported an unregistered myocardial infarction, 252 subjects
(88%) were successfully contacted, and 119 subjects provided information
that was consistent with suspected myocardial infarctions. Of these 119 subjects, 102 participants (86%) provided written in-
formed consent for their medical records to be reviewed by physicians. In these subjects, myocardial infarction was con-
firmed for 51 individuals and subsequently included in the
registry. Similarly, cases identified by the 5-y follow-up ques-
tionnaire and confirmed by hospital records were also included in
the registry. As a result, an additional 225 strokes and 93 myocardial
infarction cases were identified and reported. Of these cases, 172
additionally identified stroke and 71 additionally identified myo-
cardial infarction subjects were included in the current analyses. A
systematic search for additional fatal stroke and IHD subjects was
also conducted by reviewing death certificates. Deaths that were
a result from stroke (International Classification of Diseases, 10th
Revision codes I60–I69), IHD, or acute heart failure (codes I21–
I46, and I50) that were listed on the death certificate but had
not been registered were reviewed.

### Mortality

The underlying cause of death was defined according to the
International Classification of Diseases, 10th Revision. All death
certificates were forwarded centrally to the Ministry of Health,
Welfare and Labor and coded for the National Vital Statistics.
Registration of death is required by the Family Registration Law;
therefore, accurate reporting was assumed for the purposes of this
study.

### Statistical analysis

Participants were classified into quintiles of rice consumption.
Age-adjusted mean values and proportions of updated cardio-
vacular risk factors and population characteristics were pre-
vented according to quintiles of rice consumption. CVD
incidence and mortality were analyzed separately. For the
analysis of CVD incidence, person-years of follow-up were
calculated from the date of the starting point 1 January 1990 in
cohort I and 1 January 1993 in cohort II until the obtainment 1 of
4 possible endpoints as follows: 1) incidence of a first stroke or
first IHD event, 2) relocation from the study area, 3) the end of
the study on 31 December 2009 for cohort I and 31 December
2007 for cohort II, 4) death. For the analysis of CVD mor-
tality, person-years of follow-up were censored at the date of
death, emigration from Japan, or end of the study (31 December
2009 in both cohort I and cohort II), whichever came first. For
persons who were lost to follow-up, the last confirmed date of
their presence in the study area was used as the date of cen-
soring.

Because there were no interactions by sex for any endpoint
(Pinteraction > 0.05), analyses were done for both men and
women combined; however, we also investigated associations
separately for men and women by using Cox proportional haz-
ard modeling to assess the association between quintiles of rice
consumption with risk of CVD. For the multivariate analysis, we
adjusted for age (continuous), sex, PHC, history of hypertension,
and diabetes or the use of a lipid-lowering drug (yes or no); BMI
(quintiles); smoking status (never, ex-smoker, and current
smoker of 1–19, 20–29, or ≥30 cigarettes/d); ethanol intake
(nondrinkers, former drinkers, and weekly ethanol intake <150,
150 to <300, 300 to <450, or ≥450 g/wk); leisure-time sports
activity (≤3 d/mo, 1–2 d/wk, and ≥3 d/wk); job status (white-
collar job, blue-collar job, and unemployed); and quintiles of en-
ergy-adjusted dietary intakes of selected foods and nutrients
(seafood, meat, fruit, vegetables, soy, SFAs, and sodium); and
total caloric intake. For women, we also adjusted for meno-
pausal status and postmenopausal hormone use. We conducted
tests for trends across quintiles of rice consumption by assigning
median values for each quintile and testing the significance of
this variable.

We updated rice consumption and confounding variables by
using the baseline and 5- and 10-y follow-up questionnaire
surveys except for age, sex, and PHC. Data on nondietary vari-
ables were updated from each questionnaire. To reduce within-
subject variation and best represent a long-term diet, cumulative
averages of quintiles of total calories and energy-adjusted rice
and other dietary variables from the 3 questionnaires were ranked
on the basis of the sum of these quintile averages. Cumulative
averages of continuous dietary variables themselves were not
used because of a large drift in mean amounts of caloric and
nutrient intakes between baseline and follow-up questionnaires.
We made the last observation carried forward to impute missing
values. For example, data from the baseline questionnaire was
used to replace missing values in the 5-y follow-up questionnaire,
and values in the 5-y follow-up questionnaire were used to re-
place missing values in the 10-y follow-up questionnaire.

With the use of the cumulative average method, the incidence
of and mortality from CVD between each 5-y questionnaire cycle
were related to the cumulative average of rice consumptions
calculated from all preceding dietary measures. Sensitivity
analyses were conducted twice as follows: 1) by reanalyzing with
the use of baseline data only and 2) by relating CVD events to
most-recent dietary data. Furthermore, associations between
total dietary carbohydrate intakes and risk of CVD were also investigated.
A stratified analysis by BMI (<25 or ≥25) was also conducted, and an interaction term generated by multiplying the median of each quintile of rice consumption by BMI was used to test an effect modification by BMI. Multiple sensitivity analyses were also conducted by excluding participants with a past history of diabetes at baseline, ceasing updating rice consumption and other dietary variables if participants reported disease history in follow-up questionnaires (type 2 diabetes, hypertension, cancer, or liver or kidney disease), and restricting the age of participants to a middle-aged group (40–59 y). The analysis was conducted with SAS version 9.3 software (SAS Institute Inc). All P values were 2-sided, and P < 0.05 was regarded as statistically significant.

RESULTS
During 1,401,401 person-years of follow-up of 92,223 men and women, 4395 incident cases of stroke (1777 hemorrhagic and 2590 ischemic strokes) and 1088 incident cases of IHD were diagnosed, and during 1,428,544 person-years of follow-up, 2705 deaths that were a result of CVD (1153 stroke, 605 IHD, and 947 other CVD) were reported. Characteristics of study participants according to quintiles of rice consumption are shown in Table 1. Compared with participants who consumed less rice, participants with a high consumption of rice tended to be older, less likely to practice sports daily, and more likely to have a blue-collar job. An increased consumption of rice was associated with a lower consumption of alcohol, seafood, vegetables, fruit, meat, soy, SFAs, and sodium.

| TABLE 1 |
| Age-adjusted means and proportions of updated lifestyle, health, and dietary characteristics in Japanese men and women according to quintiles of rice consumption |

<table>
<thead>
<tr>
<th>Quintiles of rice consumption</th>
<th>1 (low)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants at risk (n)</td>
<td>16,882</td>
<td>16,911</td>
<td>18,090</td>
<td>23,543</td>
<td>15,797</td>
<td>—</td>
</tr>
<tr>
<td>Median rice consumption (g/d)</td>
<td>251 ± 43</td>
<td>326 ± 89</td>
<td>377 ± 88</td>
<td>430 ± 89</td>
<td>542 ± 127</td>
<td>—</td>
</tr>
<tr>
<td>Men (%)</td>
<td>49</td>
<td>47</td>
<td>46</td>
<td>43</td>
<td>55</td>
<td>—</td>
</tr>
<tr>
<td>Age at baseline (y)</td>
<td>50.8 ± 7.7</td>
<td>51.6 ± 7.9</td>
<td>52.1 ± 7.9</td>
<td>52.5 ± 8.0</td>
<td>52.4 ± 7.9</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 3.2</td>
<td>23.7 ± 3.3</td>
<td>23.7 ± 3.2</td>
<td>23.6 ± 3.2</td>
<td>23.4 ± 3.1</td>
<td>0.97</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>20</td>
<td>21</td>
<td>23</td>
<td>24</td>
<td>20</td>
<td>0.03</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>Ethanol intake (g/wk)</td>
<td>407 ± 396</td>
<td>298 ± 305</td>
<td>266 ± 306</td>
<td>261 ± 284</td>
<td>240 ± 264</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>23</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>23</td>
<td>0.06</td>
</tr>
<tr>
<td>Practicing sports daily (%)</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>11</td>
<td>9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blue-collar workers (%)</td>
<td>16</td>
<td>15</td>
<td>20</td>
<td>30</td>
<td>24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs (%)</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>0.02</td>
</tr>
<tr>
<td>Energy consumption (kcal/d)</td>
<td>2062 ± 1157</td>
<td>2018 ± 1064</td>
<td>2002 ± 921</td>
<td>1901 ± 778</td>
<td>2015 ± 807</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seafood consumption (g/d)</td>
<td>84 ± 104</td>
<td>82 ± 78</td>
<td>85 ± 67</td>
<td>79 ± 67</td>
<td>69 ± 59</td>
<td>0.001</td>
</tr>
<tr>
<td>Vegetable consumption (g/d)</td>
<td>509 ± 429</td>
<td>534 ± 455</td>
<td>536 ± 436</td>
<td>532 ± 391</td>
<td>450 ± 354</td>
<td>0.02</td>
</tr>
<tr>
<td>Fruit consumption (g/d)</td>
<td>222 ± 242</td>
<td>217 ± 229</td>
<td>216 ± 208</td>
<td>205 ± 184</td>
<td>166 ± 184</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Meat consumption (g/d)</td>
<td>70 ± 88</td>
<td>70 ± 86</td>
<td>66 ± 73</td>
<td>64 ± 62</td>
<td>50 ± 52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Soy consumption (g/d)</td>
<td>96 ± 166</td>
<td>94 ± 148</td>
<td>97 ± 168</td>
<td>91 ± 150</td>
<td>71 ± 122</td>
<td>0.0003</td>
</tr>
<tr>
<td>Carbohydrate consumption (g/d)</td>
<td>234 ± 73</td>
<td>252 ± 63</td>
<td>264 ± 57</td>
<td>275 ± 48</td>
<td>301 ± 50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total dietary fiber consumption (g/d)</td>
<td>15.3 ± 12.8</td>
<td>13.6 ± 8.4</td>
<td>14.4 ± 9.2</td>
<td>12.6 ± 6.7</td>
<td>11.9 ± 7.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Saturated fatty acid consumption (g/d)</td>
<td>19 ± 10.0</td>
<td>18 ± 9.0</td>
<td>17 ± 8.0</td>
<td>16 ± 7.0</td>
<td>13 ± 6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protein consumption (g/d)</td>
<td>75 ± 25</td>
<td>74 ± 21</td>
<td>74 ± 22</td>
<td>73 ± 17</td>
<td>66 ± 16</td>
<td>0.0004</td>
</tr>
<tr>
<td>Sodium consumption (mg/d)</td>
<td>4552 ± 2153</td>
<td>4671 ± 2065</td>
<td>4704 ± 1971</td>
<td>4731 ± 1807</td>
<td>4274 ± 1800</td>
<td>0.03</td>
</tr>
</tbody>
</table>

1 Chi-square test was used for categorical variables; ANOVA was used for continuous variables.
2 Mean ± SD (all such values).
Furthermore, associations between dietary intake of total carbohydrate and risk of CVD were examined. In a multivariable model adjusted for age, sex, PHC, history of hypertension, history of diabetes, use of cholesterol-lowering drugs, BMI, smoking status, alcohol intake, leisure-time sports activity, occupation, intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use.

### TABLE 2
Multivariable HRs (95% CIs) of incident cardiovascular disease according to quintiles of rice consumption

<table>
<thead>
<tr>
<th>Quintiles of daily rice consumption</th>
<th>1 (low)</th>
<th>2</th>
<th>3</th>
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<th>P-trend$^1$</th>
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<td>16,911</td>
<td>18,090</td>
<td>23,543</td>
<td>15,797</td>
<td>—</td>
</tr>
<tr>
<td>Person-years</td>
<td>250,899</td>
<td>253,985</td>
<td>279,828</td>
<td>371,990</td>
<td>244,699</td>
<td>—</td>
</tr>
<tr>
<td>Total stroke Cases (n)</td>
<td>789</td>
<td>985</td>
<td>777</td>
<td>1033</td>
<td>838</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.15 (0.98, 1.27)</td>
<td>0.82 (0.75, 1.01)</td>
<td>0.81 (0.74, 1.09)</td>
<td>0.95 (0.86, 1.14)</td>
<td>0.36</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>1.07 (0.93, 1.17)</td>
<td>0.94 (0.85, 1.08)</td>
<td>0.93 (0.84, 1.13)</td>
<td>1.01 (0.90, 1.14)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hemorrhagic stroke Cases (n)</td>
<td>336</td>
<td>388</td>
<td>318</td>
<td>426</td>
<td>309</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.11 (0.96, 1.29)</td>
<td>0.81 (0.70, 1.05)</td>
<td>0.81 (0.70, 1.03)</td>
<td>0.90 (0.84, 1.11)</td>
<td>0.43</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>1.05 (0.90, 1.22)</td>
<td>0.95 (0.81, 1.12)</td>
<td>0.95 (0.81, 1.11)</td>
<td>0.96 (0.79, 1.15)</td>
<td>0.51</td>
</tr>
<tr>
<td>Ischemic stroke Cases (n)</td>
<td>450</td>
<td>563</td>
<td>452</td>
<td>604</td>
<td>512</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.08 (0.94, 1.26)</td>
<td>0.93 (0.79, 1.04)</td>
<td>0.92 (0.79, 1.12)</td>
<td>0.98 (0.88, 1.13)</td>
<td>0.27</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>1.07 (0.92, 1.23)</td>
<td>0.99 (0.81, 1.07)</td>
<td>0.99 (0.81, 1.16)</td>
<td>1.05 (0.90, 1.22)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

$^1$ Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. $^2$ Estimated by using Cox’s proportional hazard model adjusted for age and sex.

### TABLE 3
Multivariable HRs (95% CIs) of mortality from cardiovascular disease according to quintiles of rice consumption

<table>
<thead>
<tr>
<th>Quintiles of daily rice consumption</th>
<th>1 (low)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P-trend$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants at risk (n)</td>
<td>16,838</td>
<td>16,802</td>
<td>18,168</td>
<td>23,675</td>
<td>15,740</td>
<td>—</td>
</tr>
<tr>
<td>Person-years</td>
<td>255,254</td>
<td>258,247</td>
<td>285,966</td>
<td>379,863</td>
<td>249,212</td>
<td>—</td>
</tr>
<tr>
<td>Total stroke Cases (n)</td>
<td>402</td>
<td>237</td>
<td>221</td>
<td>276</td>
<td>217</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.09 (0.91, 1.32)</td>
<td>0.96 (0.78, 1.17)</td>
<td>0.90 (0.74, 1.09)</td>
<td>1.06 (0.87, 1.29)</td>
<td>0.61</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>1.07 (0.88, 1.13)</td>
<td>0.99 (0.80, 1.22)</td>
<td>0.95 (0.77, 1.19)</td>
<td>1.08 (0.84, 1.38)</td>
<td>0.56</td>
</tr>
<tr>
<td>Ischemic heart disease Cases (n)</td>
<td>113</td>
<td>108</td>
<td>112</td>
<td>147</td>
<td>125</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>0.89 (0.69, 1.16)</td>
<td>0.80 (0.62, 1.04)</td>
<td>0.78 (0.61, 1.09)</td>
<td>0.94 (0.73, 1.22)</td>
<td>0.55</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>0.81 (0.61, 1.06)</td>
<td>0.93 (0.70, 1.23)</td>
<td>0.85 (0.64, 1.12)</td>
<td>0.93 (0.68, 1.27)</td>
<td>0.42</td>
</tr>
<tr>
<td>Other cardiovascular disease Cases (n)</td>
<td>172</td>
<td>187</td>
<td>182</td>
<td>218</td>
<td>188</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.01 (0.82, 1.24)</td>
<td>0.85 (0.69, 1.12)</td>
<td>0.83 (0.64, 1.09)</td>
<td>0.94 (0.76, 1.15)</td>
<td>0.33</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>0.93 (0.75, 1.16)</td>
<td>0.96 (0.77, 1.20)</td>
<td>0.85 (0.67, 1.14)</td>
<td>0.91 (0.71, 1.17)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total cardiovascular disease Cases (n)</td>
<td>487</td>
<td>532</td>
<td>515</td>
<td>641</td>
<td>530</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)$^2$</td>
<td>1.00 (reference)</td>
<td>1.02 (0.90, 1.15)</td>
<td>0.86 (0.76, 1.07)</td>
<td>0.78 (0.69, 1.06)</td>
<td>0.94 (0.83, 1.10)</td>
<td>0.19</td>
</tr>
<tr>
<td>HR (95% CI)$^3$</td>
<td>1.00 (reference)</td>
<td>0.96 (0.85, 1.09)</td>
<td>1.00 (0.88, 1.15)</td>
<td>0.81 (0.80, 1.11)</td>
<td>0.97 (0.84, 1.13)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

$^1$ Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. $^2$ Estimated by using Cox’s proportional hazard model adjusted for age and sex.

Estimated by using Cox’s proportional hazard model adjusted for age; sex; public health center area; history of hypertension; history of diabetes; use of lipid-lowering drugs; BMI; smoking status; ethanol intake; leisure-time sports activity; occupation; intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use.
intake, HR (95% CIs) in the quintile with the highest carbohydrate consumption compared with the quintile with the lowest consumption were 0.89 (0.78, 1.12; P-trend = 0.33) for risk of incident stroke, 1.30 (0.88, 1.87; P-trend = 0.19) for risk of incident IHD, and 0.88 (0.69, 1.12; P-trend = 0.26) for mortality from total CVD (data not shown in tables).

Associations of rice consumption with risk of incident stroke and IHD and mortality from stroke, IHD, and other CVD after BMI (<25 or ≥25) stratification was investigated (Table 4). There was no interaction with BMI for any endpoint, and results did not change materially in both BMI strata regarding the incidence of and mortality from CVD.

**DISCUSSION**

In this large Japanese cohort, no significant lower or higher risk of CVD incidence or mortality with higher rice consumption was observed. In addition, there was no clear evidence of differences in risk of CVD incidence or mortality between lean and overweight men or women.

There has been a great deal of speculation about the association of white rice with risk of type 2 diabetes, stroke, and IHD (5–7, 12, 17–19, 29, 30). Similar to the current study, 2 previous Japanese-cohort studies did not associate rice consumption with mortality from total or ischemic stroke in men or women (12, 18). However, in an age-only adjusted model, a positive trend was seen for hemorrhagic stroke in Japanese women in the study of Oba et al (12), with an HR (95% CI) in the quartile with the highest carbohydrate intake compared with the quintile with the lowest intake, 1.16; 95% CI, 0.99–1.36; P-trend = 0.16). However, in that study, the follow-up period was short (only 6 y), the sample size in rice-consumption quartile groups was limited (6 cases in the reference group), and the model did not address possible confounding factors, which may have contributed to an inaccurate measure of real risk.

In the current study, no association between rice consumption and risk of IHD incidence or mortality was shown, which was consistent with findings that were based on studies in Italian men and women (17). In contrast, rice was inversely associated with risk of mortality from IHD in men in another Japanese study [the Japan Collaborative Cohort (JACC) study (18)], whereas in a recent Chinese study; a combination of refined rice and wheat products were positively associated with the incidence of IHD (13). Differences between current study findings and those of the JACC or Chinese study may have been attributed to the lack of multiple measurements of dietary variables. Dietary and nondietary variables were measured once at baseline in the JACC and Chinese studies, whereas in this current study, data were updated through the use of 3 questionnaires, each 5 y apart. The use of data at only one point of time may tend to underestimate or overestimate associations, particularly when follow-up years are extensive. Moreover, the mean rice consumption (389 g/d) in the current study differed from that (511 g/d) in the JACC study. An additional factor to be considered was that rice in the current study provided 42% of total carbohydrate intake and 25% of total caloric intake, whereas 70% of carbohydrate and 60–70% of all caloric intakes in the Chinese study came from rice (13).

Rice consumption in the JPHC study was positively associated with risk of type 2 diabetes in women (6). However, on the basis of a recent Spanish cohort study, an inverse association between rice consumption and a 6-y incidence of type 2 diabetes was also shown (7). Because diabetic patients are often advised to reduce carbohydrate intake, they might change their rice consumption habits. However, in a sensitivity analysis that excluded participants in the current cohort who reported a history of diabetes at baseline (n = 2046), we showed no evidence of an association between rice consumption and risk of CVD. Multivariable HRs (95% CIs) for risk of incident stroke and IHD were 1.09 (0.84, 1.16; P-trend = 0.47) and 0.99 (0.79, 1.44; P-trend = 0.66), respectively.

Previously, Japanese men and women of different ages and BMIs showed different associations between rice consumption and mortality from CVD (12, 18). Overweight and obese individuals and those who developed some diseases may have changed their dietary habits as a result of diagnoses and treatments. However, results of the current study did not change materially when we restricted participants’ ages to a middle-age group (40–59 y) or stratified groups by BMI. In a sensitivity analysis that ceased updating rice consumption and other dietary variables if participants reported a disease history in the 5- or 10-y follow-up questionnaire (type 2 diabetes, hypertension, cancer, or liver or kidney diseases), rice consumption was still not associated with risk of CVD incidence or mortality. In the current study, there were no interactions with sex for any endpoint, and results did not change materially when men and women were analyzed separately. However, trends tended to be inverse in men, whereas the same trends tended to be positive in women. Lipoprotein changes in response to low-fat and high-carbohydrate diets differ according to sex, with greater increases in triglycerides and VLDL-cholesterol concentrations and greater decreases in HDL-cholesterol concentrations in women than in men (31). However, we should interpret these trends carefully because of the lack of clear explanations on the basis of biology or plausible mechanisms for previously observed sex differences in associations between rice consumption and risk of type 2 diabetes or CVD.

Possible reasons to explain why white rice consumption might not be associated with risk of CVD despite its positive association with risk of type 2 diabetes may be because, during the refining process, white rice loses much of its content of insoluble fiber, magnesium, vitamins, lignans, phytoestrogens, and phytic acid (2, 5), and deficiencies of these nutrients are more related to diabetes risk (32). In addition, because white rice is free of cholesterol (3) and low in sodium, its consumption, contrary to providing risk of CVD, was actually used as an aid to treat hypertension (4). In a Chinese follow-up study, there were no associations between rice consumption and plasma triglycerides concentrations or risk of metabolic syndrome. There was a 42% decrease in risk of hypertension with high rice consumption (19). These effects on lipid profiles and blood pressure are expected not to increase CVD risk in the Japanese population (33).

Although epidemiologic evidence has shown positive associations between glycemic load (GL) and glycemic index (GI) with risk of CVD (9–13) and type 2 diabetes (34), overall carbohydrate intake is less strongly related to these diseases, with studies that showed no association (9, 12, 17, 34), a positive association (10, 11, 13), and an inverse association (35, 36). Furthermore, adverse metabolic effects of high carbohydrate intake or dietary GL have been greatly exaggerated in the presence of an underlying insulin resistance (9). Greater BMI has strongly been associated with insulin resistance (37).
<table>
<thead>
<tr>
<th></th>
<th>BMI &lt;25 kg/m² (n = 68,780)</th>
<th></th>
<th>BMI ≥ 25 kg/m² (n = 22,443)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quintile 1 (low)</td>
<td>Quintile 2</td>
<td>Quintile 3</td>
<td>Quintile 4</td>
</tr>
<tr>
<td>Participants at risk (n)</td>
<td>13,071</td>
<td>12,632</td>
<td>13,403</td>
<td>17,484</td>
</tr>
<tr>
<td>Person-years</td>
<td>194,444</td>
<td>189,164</td>
<td>206,466</td>
<td>275,269</td>
</tr>
<tr>
<td>Incident stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>581</td>
<td>673</td>
<td>581</td>
<td>715</td>
</tr>
<tr>
<td>HR (95% CI) &amp; P-trend²</td>
<td>0.97 (0.86, 1.10)</td>
<td>0.89 (0.79, 1.01)</td>
<td>0.97 (0.85, 1.12)</td>
<td>0.47</td>
</tr>
<tr>
<td>Incident IHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>138</td>
<td>146</td>
<td>145</td>
<td>194</td>
</tr>
<tr>
<td>HR (95% CI) &amp; P-trend²</td>
<td>0.91 (0.71, 1.16)</td>
<td>0.99 (0.77, 1.27)</td>
<td>1.01 (0.79, 1.30)</td>
<td>1.09 (0.82, 1.45)</td>
</tr>
<tr>
<td>Total stroke mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>172</td>
<td>188</td>
<td>181</td>
<td>216</td>
</tr>
<tr>
<td>HR (95% CI) &amp; P-trend²</td>
<td>1.01 (0.82, 1.25)</td>
<td>1.05 (0.82, 1.25)</td>
<td>0.93 (0.75, 1.17)</td>
<td>0.99 (0.76, 1.28)</td>
</tr>
<tr>
<td>IHD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>93</td>
<td>81</td>
<td>87</td>
<td>125</td>
</tr>
<tr>
<td>HR (95% CI) &amp; P-trend²</td>
<td>0.79 (0.58, 1.07)</td>
<td>0.91 (0.67, 1.25)</td>
<td>0.92 (0.68, 1.25)</td>
<td>0.93 (0.66, 1.32)</td>
</tr>
<tr>
<td>Other CVD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases (n)</td>
<td>155</td>
<td>158</td>
<td>154</td>
<td>169</td>
</tr>
<tr>
<td>HR (95% CI) &amp; P-trend²</td>
<td>0.85 (0.64, 1.14)</td>
<td>0.83 (0.61, 1.13)</td>
<td>0.86 (0.63, 1.16)</td>
<td>0.80 (0.56, 1.15)</td>
</tr>
</tbody>
</table>

¹ HRs (95% CIs) were estimated by using Cox’s proportional hazard model adjusted for age; sex; public health center area; history of hypertension; history of diabetes; use of lipid-lowering drugs; BMI; smoking status; ethanol intake; leisure-time sports activity; occupation; intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use. CVD, cardiovascular disease; IHD, ischemic heart disease.

² Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. P-values for an interaction term generated by multiplying the median of each quintile of rice consumption by BMI were >0.05 for all endpoints.
Japanese populations have a relatively lower BMI than that of Chinese or Western populations, which may explain the null association between total carbohydrate intake and risk of CVD in our cohort. The use of GI and GL were considered better indicators for the relation of the quantity and quality of carbohydrates to risk of chronic disease (9). Regrettably, data on GI and GL were not yet available for the current study.

To the best of our knowledge, this is the first prospective cohort study of white rice consumption and incident risk of CVD. Some strengths of the current study were its population-based prospective design involving a large sample size as well as the use of a validated FFQ. Analyses contained in the current study were based on calorie-adjusted measures of rice consumption. Changes in rice consumption over time were considered, and enhanced data from follow-up surveys were able to capture consumed amounts more accurately. Furthermore, dietary data of the Japanese population allowed an assessment of any potential associations at relatively high amounts of rice consumption. Several sensitivity analyses were conducted that yielded similar results.

Limitations to this study included a potential misclassification that arose from gathering self-reported data. However, self-reported data such as height, weight, and blood pressure may have been reasonably accurate because nationwide annual health screenings conducted since 1992 in Japan produced similar results (38). We included 1405 subjects with missing information on rice consumption on follow-up surveys in our analysis after the imputation of their rice consumption from the preceding questionnaire which may have raised a source of selection bias. However, in addition to the small number (1.1% of the total sample), there were no significant differences in CVD risk profiles between subjects with or without missing data. Last, because FFQs did not contain data on the consumption of brown grain or brown rice, an isocaloric analysis describing results when total caloric intake is fixed could not be conducted. However, because brown rice or other whole grains are not commonly used in Japan, whether risk would be lower if the white rice was replaced by these foods would not have easily been determined.

In conclusion, contrary to various expectations that an inverse or a positive association between rice consumption with risk of CVD may exist, our large Japanese cohort showed that rice consumption is not associated with risk of CVD incidence or mortality in Japanese men and women. Despite the growing evidence for a positive association between white rice consumption and risk of type 2 diabetes, rice consumption adds no evidence for a positive association between white rice consumption and mortality in Japanese men and women. Although the Japanese population showed higher consumption of carbohydrates compared to the general population, the results of this study indicate that rice consumption may be negatively associated with risk of CVD.

Several sensitivity analyses were conducted that yielded similar results. We thank the Japan Cardiovascular Research Foundation for offering ESE a research resident grant for his postdoctoral study and Daniel K Ward for his assistance in editing the manuscript. Members of the JPHC-based Prospective Study Group are as follows: ST (JPHC study principal investigator), MI, T Sobe, and T Hanaoka, National Cancer Centre, Tokyo; J Ogata, S Baba, T Mannami, A Okayama, and YK, National Cardiovascular Centre, Osaka; K Miyakawa, F Saito, A Koizumi, Y Sano, I Hashimoto, and T Ikuta, Osaka Medical Centre for Health Science and Promotion, Osaka; E Maruyama, HPV, N Yasuda, Kochi University, Kochi; and S Kono, Kyushu University, Fukuoka.

The authors’ responsibilities were as follows—HI, KY, YK, IS, HY, NS, MI, and ST: designed the research; ESE and H: conducted the research; ESE: analyzed data; ESE and H: wrote the manuscript and had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES