Combined Cardiovascular Risk Factors and Outcome
—— NIPPON DATA80, 1980–1994 ——

Yasuyuki Nakamura, MD; Takako Yamamoto, MD*; Tomonori Okamura, MD*; Takashi Kadawaki, MD*; Takehito Hayakawa, PhD**; Yoshikuni Kita, PhD*; Shigeyuki Saitoh, MD†; Akira Okayama, MD††; Hirotsugu Ueshima, MD*; for the NIPPON DATA 80 Research Group

Background To examine the prognostic significance of the high-risk group with combined cardiovascular risk factors in the Japanese, we analyzed the relationship between the high-risk group with combined risks and coronary heart disease (CHD) and stroke mortality using the NIPPON DATA80 database.

Methods and Results At baseline in 1980, those of age ≥30 years were randomly selected and 4,144 men and 5,318 women without CHD and/or stroke at baseline were followed for 14 years. The cutoff values for risk components obtained heuristically by Cox analysis were hypertension (systolic ≥130, or diastolic ≥85 mmHg, or on antihypertensive drugs), hypercholesterolemia (total cholesterol ≥200 mg/dl), hyperglycemia (≥130 mg/dl, or self-reported diabetes) and obesity (body mass index ≥27 kg/m²). Subjects were divided into 3 groups (0, 1–2 and 3–4 risks). Compared with those men in the risk 0 group, the hazard ratios in men in the risk 3–4 for CHD mortality was 8.04 (95% confidence interval: 1.03–62.6), and the stroke mortality was 5.06 (1.53–16.7). In women, no statistically significant difference was found due to a lesser number of events.

Conclusion The high-risk group with combined risk factors is important risk for Japanese men. (Circ J 2006; 70: 960–964)

Key Words: Cohort study; Coronary heart disease; Risk factors; Stroke

Cardiovascular risk factors, such as dyslipidemia, hypertension, hyperglycemia and obesity, are consistent and common but largely undertreated and undercontrolled in many countries, although it is known that these risk factors often cluster together. This clustering is now considered to be the “metabolic syndrome”, which is closely related to insulin resistance. Cutoff values for cardiovascular risk factors have been derived either empirically or from the results of cross-sectional studies, but ideally, such cutoff values should be derived from the data of longitudinal cohort studies, so that risk factors have prognostic implications. Furthermore, the cutoff values for these risk factors and the prognostic significance of combined risk factors have not yet been reported in Asian populations, where coronary heart disease (CHD) mortality and obesity are relatively rare, but susceptibility to diabetes mellitus has been reported to be higher. The individual cutoff values should be determined for different populations, so to examine the prognostic significance of the high-risk group with combined risk factors we analyzed the relationship between combined cardiovascular risk factors and CHD and stroke mortality using the database of the National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged, 1980 (NIPPON DATA80), which includes more than 10,000 subjects in Japan who were followed for 14 years.

Methods

Subjects

The subjects in this cohort were participants in the 1980 National Survey on Circulatory Disorders; the detailed methods of the NIPPON DATA80 have been described previously but are summarized here. A total of 10,546 community-based subjects aged ≥30 years in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of a medical history, physical examinations, blood tests and a self-administered questionnaire on lifestyle. The cohort was followed until 1994.

To clarify the causes of death, we used the National Vital Statistics.

Of the 10,546 subjects, a total of 1,084 were excluded for the following reasons: past history of CHD or stroke (n=166), missing information on the baseline survey (n=48), lost to follow-up (n=870). We analyzed the remaining 9,462 subjects (4,144 men, 5,318 women). Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Biochemical and Baseline Examinations

The baseline surveys were conducted by public health centers. Systolic and diastolic blood pressures (SBP, DBP)
were measured by trained operators using a standard mercury sphygmomanometer on the subjects’ right arm while the subjects were seated and after they had rested for more than 5 min. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m).

A lifestyle survey was carried out using a self-administered questionnaire. Non-fasting blood samples were drawn and centrifuged within 60 min of collection, and then stored at −70°C until analysis. Total cholesterol was analyzed in a sequential auto-analyzer (SM-A12/60; Technicon, Tarrytown, NY, USA) at a single laboratory (Osaka Medical Center for Health Science and Promotion), which is a member of the Cholesterol Reference Method Laboratory Network.15 The serum concentration of glucose was measured using the cupric-neocuproline method.16

### Combined Cardiovascular Risk Factors

The previous cutoff values used for the definition of metabolic syndrome6,7 were not applied in the present study for the following reasons. Waist girth was not measured during the baseline examinations in 1980. The modified WHO definition uses BMI ≥30 kg/m² as a criteria for abdominal obesity, but because the average BMI for Japanese adult men and women is around 23 kg/m², there are very few subjects whose BMI is more than 30 kg/m².17–20 Non-fasting blood samples were drawn in the present study, and direct measurement of high density lipoprotein (HDL) cholesterol was not performed. Therefore, we selected 4 components of the combined risk factors, namely, obesity, hyperglycemia, hypercholesterolemia and hypertension. The cutoff value for each component was determined heuristically using the mortality data described below. We considered those who were on antihypertensive medication as having hypertension, and those who with self-reported diabetes mellitus as having hyperglycemia. We then divided the study subjects into 3 groups: risk 0 for subjects who had none of the above components, risk 1–2 for subjects who had 1 or 2 of the components, and risk 3–4 for subjects who had 3 or 4 of the above components.

### Statistical Analyses

SAS version 8.02 for WINDOWS (SAS Institute Inc, Cary, NC, USA) was used throughout the analyses. Men and women were analyzed separately. The chi-square test was used to compare dichotomous variables. To compare the means among the 3 groups, one-way analysis of vari-

### Table 1 Results of Principal Component Analysis Among 3,820 Men and 4,857 Women Not Taking Medication (NIPPON DATA80: 1980–1994)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men Factor 1</th>
<th>Men Factor 2</th>
<th>Women Factor 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>0.44</td>
<td>0.65</td>
<td>0.50</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.84</td>
<td>−0.37</td>
<td>0.86</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.88</td>
<td>−0.18</td>
<td>0.85</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.33</td>
<td>0.72</td>
<td>0.44</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>0.24</td>
<td>−0.25</td>
<td>0.31</td>
</tr>
<tr>
<td>Total variance</td>
<td>0.37</td>
<td>0.23</td>
<td>0.40</td>
</tr>
<tr>
<td>Cumulative variance</td>
<td>0.37</td>
<td>0.60</td>
<td>0.40</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

### Table 2 Results of Heuristic Analysis in Men to Obtain the Cutoff Values for Risk Components Among 4,144 Men (NIPPON DATA80: 1980–1994)

<table>
<thead>
<tr>
<th>Risk 3–4 (%)</th>
<th>CHD HR (p)</th>
<th>Stroke HR (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>15</td>
<td>6.94 (0.064)</td>
</tr>
<tr>
<td>27</td>
<td>13</td>
<td>8.04 (0.046)</td>
</tr>
<tr>
<td>28</td>
<td>11.5</td>
<td>9.17 (0.035)</td>
</tr>
<tr>
<td>BG (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>17.5</td>
<td>6.12 (0.081)</td>
</tr>
<tr>
<td>130</td>
<td>13</td>
<td>8.04 (0.046)</td>
</tr>
<tr>
<td>140</td>
<td>10</td>
<td>7.11 (0.068)</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>2.39 (0.144)</td>
</tr>
<tr>
<td>200</td>
<td>13</td>
<td>8.04 (0.046)</td>
</tr>
<tr>
<td>220</td>
<td>7.8</td>
<td>10.29 (0.028)</td>
</tr>
<tr>
<td>SBP/DBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120/80</td>
<td>14.9</td>
<td>&gt;50 (0.986)</td>
</tr>
<tr>
<td>130/85</td>
<td>13</td>
<td>8.04 (0.046)</td>
</tr>
<tr>
<td>140/90</td>
<td>10.3</td>
<td>3.20 (0.053)</td>
</tr>
</tbody>
</table>

Fixing the values of 3 components, value of the 4th component was varied categorically and the Cox analyses were performed. Hazard ratios (HR) with p values for CHD and stroke mortality were compared. The risk 0 group was used as the reference group. The Cox analyses were repeated until the lowest cutoff value for each component that had a prognostic significance for CHD and/or stroke mortality was obtained. The obtained cutoff values were BMI ≥27 kg/m², BG ≥130 mg/dl, TC ≥200 mg/dl, SBP/DBP ≥130/85 mmHg for men. Risk 3–4= subjects who had 3 or 4 of the risk (risks are: hypertension: SBP ≥130 mmHg, or DBP ≥85 mmHg, or on anti-hypertensive drugs; hypercholesterolemia: TC ≥220 mg/dl; hyperglycemia: BG ≥130 mg/dl or self-reported diabetes mellitus; obesity: BMI ≥27 kg/m²).

### CHD, coronary heart disease; BG, blood glucose; TC, total cholesterol. Other abbreviations see in Table 1.

The multivariate-adjusted hazard ratios for CHD, and stroke mortality were calculated using the Cox proportional hazard model, including age, cigarette smoking (currently smoking or not), and alcohol intake (drinkers or non-drinkers) as covariates. The risk 0 group was used as the reference group. The cutoff values for each of the 4 components were determined heuristically using the Cox analyses on CHD and stroke mortality. Namely, fixing the values of 3 components, the value of the 4th component was categorically varied and the Cox analyses were performed. The Cox analyses were repeated until we found the lowest cutoff value for each component that had prognostic significance for CHD and/or stroke mortality. The entered values for each component were BMI: from 25 to 30 kg/m² with 1 kg/m² increments; blood glucose: from 100 to 160 mg/dl with 10 mg/dl increments; total cholesterol: from 180 to 260 mg/dl with 20 mg/dl increments; SBP/DBP: 120/80, 130/85 and 140/90 mmHg. Because most of the analyses in women did not yield cutoff values that had prognostic significance, the cutoff values for men were applied in the analyses of women.

Hazard ratios for the association of CHD and stroke mortality with the component conditions were analyzed by the Cox proportional hazard model as above. Tests of linear
trends across risk groups were conducted by assigning an ordinal value to each number risk (0 to 4) and modeling this as a continuous variable in separate Cox proportional hazard models.

All p values were two-tailed, and p<0.05 was considered significant. Data are presented as means ± SDs unless stated otherwise.

Results

Principal Components

The results of principal component analysis of the risk factors are shown in Table 1. In men, a 2-component solution explained 60% of the common variance in the data set. The component has large positive loadings (≥0.40) for 3 of the 5 risk factor components, and the second has large positive loadings for 2 of the 5 risk factor components. One component, BMI, shows overlap. In women, a one-component solution explained 40% of the common variance in the data set. The component has large positive loadings for 4 of the 5 risk factors. In both men and women, loadings for glucose were not large.

Cutoff Values for Risk Components

The obtained categorical cutoff values for the risk components by heuristic analyses were BMI: 27 kg/m², blood glucose =130 mg/dl, total cholesterol =200 mg/dl, and SBP/DBP =130/85 mmHg for men. Table 2 shows the results of heuristic analyses in men to obtain the cutoff values for the risk components. Only the results of 3 representative categorical values for each component are shown. The prevalence of the risk 3–4 group in %, hazard ratios and p values for CHD and stroke mortality are shown. It can be seen that selecting the cutoff values for the 4 components satisfied prognostic significance for both CHD and stroke mortality in men.

We did not have appropriate cut-offs for the women; therefore, we used the same cut-offs as for the men.

Baseline Characteristics

The baseline characteristics for men and women in each risk group are shown in Table 3. Age was significantly greater in the higher risk groups for men and women. Smoking was less in the higher risk groups for men and drinking was less in the higher risk groups for women. BMI, SBP, DBP, blood glucose and total cholesterol were significantly higher in the higher risk groups by definition.
If the high risk group is defined here as those who have 3 or 4 risk components, its prevalence was 13.0% for men and 16.8% for women.

**Combined Risks and Outcome: Multivariate Cox Analyses**

Case number, unadjusted mortality per 1,000 person-years, and hazard ratios of CHD, and stroke mortality by multivariate Cox analyses adjusted for age, smoking and drinking are shown in Table 4 for both men and women. In men, for those in the risk 3–4 group, the hazard ratio of CHD was 8.04 and that of stroke was 5.06, in comparison with the risk 0 group. Both trends were significant (trend p<0.0001 and 0.0002). Men in the risk 1–2 group carried intermediate risks for CHD and stroke.

However, in women, no significant trend was noted for CHD or stroke mortality, probably because of lower mortality.

**Discussion**

This prospective population-based cohort study in Japan reports an association of the high-risk group with CHD and stroke mortality. The previously proposed cut-off values for cardiovascular risk factors cannot be applied to non-Western populations because, for instance, the average BMI and waist circumference for Asians are smaller. Several studies in Asians report that for the definition of obesity in Asians the cutoff value for BMI is 23 kg/m² and for waist circumference is 90 cm for men and 80 cm for women.

In the present study, we selected hypertension, hypercholesterolemia, hyperglycemia and obesity as the components of the combined cardiovascular risk, and the cutoff values for each of these were determined heuristically using Cox analyses of CHD and stroke mortality. By the present definition, the prevalence of the high-risk group with 3 or more risk factors was 13.0% for Japanese men and 16.8% for women in 1980. Although CHD mortality in Japan is relatively low in comparison with that of the Western population, the impact of the combined risk factors on CHD mortality in men was significant, with a multivariate adjusted hazard ratio of 8.04.

The lack of prognostic significance of the combined cardiovascular risk in women in the present study is probably due to a lower incidence of CHD and stroke compared with men.

**Study Limitations**

The method of obtaining the categorical cutoff values for the risk components and the method of evaluating the prognostic significance of the newly obtained diagnostic criteria of the combined risks were the same, namely Cox analyses. This may appear to be a circular tautology. However, the second Cox analysis was applied merely to show the magnitude of the prognostic significance of the criteria. Applying these criteria to a different population or to the same study with a longer follow-up may be needed in the future to verify this method. Another method of obtaining the cutoff values may be to apply the recursive partitioning method. This method may be quite valuable in handling gene expression data for tumor and cell classification but may not be useful when the variables are confounded by each other, such as blood pressure, BMI, total cholesterol concentrations, blood glucose and age, as in the present study. In fact, trial use of this method for the present data resulted in impractical cutoff values, with one variable having different values that appeared at more than 2 branches of the tree.

The results of principal component analysis in this study suggest clustering of 4 of the 5 components (BMI, SBP, DBP, total cholesterol and non-fasting glucose) except for 1 component, non-fasting glucose. This may be due to the fact that we did not have fasting glucose data. We also need more variables, such as HDL-cholesterol, triglyceride concentrations, an index of insulin resistance, and inflammation markers, to examine the clustering and to find the primary unifying underlying abnormality of the clustered risk factors, as performed in recent studies.

Non-fasting blood samples were used in the present study, and direct measurement of HDL-cholesterol was not performed. Therefore, we did not have measurements for fasting blood glucose, triglycerides or HDL-cholesterol, which are other important components of metabolic syndrome. Furthermore, waist circumference measurements will be required in future studies.

We used mortality data as endpoints, which might have led to misclassification of the causes of death. However, it has been reported that the death-certificate diagnosis of stroke and cancer in Japan is quite accurate although it has also been reported that most cases of sudden cardiac death tend to be described on Japanese death certificates as “coronary heart disease”, “heart failure” or “unknown cause”. Furthermore, mortality statistics for coronary heart disease by the end of 1994 may have been underestimated using ICD9, since deaths coded as “heart failure” may hide certain coronary events.

**Conclusion**

Cutoff values for cardiovascular risk factors have been obtained and the defined high-risk group with combined risk factors is important risk for Japanese men.

**Acknowledgments**

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**References**