Cerebral hemorrhage was previously the leading cause of death in Japan, but has substantially decreased largely because of a reduction in dietary salt intake and better control of hypertension. On the other hand, a high-fat, high-protein diet and reduced physical activity are anticipated to increase the incidence of coronary artery disease (CAD), as has happened in Western countries. In fact, both the total cholesterol concentration and body weight of the Japanese population have continued to rise over the past 20 years, and the prevalence of diabetes mellitus has also increased. In Western countries, many epidemiological studies have investigated the incidence of acute myocardial infarction (AMI) and coronary risk factors, and large scale interventional trials have been done on the primary and secondary prevention of CAD. The World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (WHO MONICA) Project was a well-designed epidemiological study that examined the incidence and case fatality rate from CAD in 37 populations from 21 countries but unfortunately, it did not include Japan where there have been limited regional reports. Because of the lack of a large-scale assessment of morbidity or mortality from myocardial infarction (MI) among the Japanese working population, we initiated the Morbidity of Myocardial Infarction Multicenter Study in Japan (3M Study) in 1997. Here we describe the study design and clarify the event rates for MI and coronary death, as well as acute case fatality rates, for each age category based on the WHO MONICA criteria.

Methods

Registration of MI and sudden death was done by full-time occupational physicians in Japan. Among 133,099 workers (109,550 men, 23,549 women) from 41 workplaces (April 1994 to March 1997) and 257,440 workers (207,310 men, 50,130 women) from 76 workplaces (April 1997 to March 2000), 297 fatal and nonfatal cardiac events were registered. The definitions of MI and coronary death followed the criteria of the WHO MONICA Project. The event rate in men rose sharply around the age of 45 years. Using definition 1 (fatal definite + fatal possible + fatal unclassifiable + nonfatal definite), the age-standardized annual event rate and case fatality rate for men aged 35–64 years was 40.2 per 100,000 persons and 22.2%, respectively. These figures were significantly lower compared with those from Western reports and were also lower than previously reported for Japanese communities.

Conclusion

The Morbidity of Myocardial Infarction Multicenter Study in Japan revealed a surprisingly low incidence of coronary events, which may be attributable to prevention and early treatment of coronary risk factors among company workers in Japan.

Key Words: Annual health examination; Morbidity; Myocardial infarction; Occupational physician; Workplace

(Received March 1, 2005; revised manuscript received April 12, 2005; accepted April 19, 2005)

Osaka Health Promotion and Medical Center, Mizuho Financial Group, Osaka, Japan

Mailing address: Kazuhiko Hirobe, MD, Osaka Health Promotion and Medical Center, Mizuho Financial Group, 4-2-1 Imabashi, Chuo-ku, Osaka 541-0042, Japan. E-mail: hirobe-f@fa2.so-net.ne.jp
Event Registration and Background Research

In November 1996, the “MI and sudden death registration form” was sent to each of the 76 collaborating medical center for recording cases of MI and sudden death of unknown cause for 3 years between April 1997 and March 2000. From these, 41 that could provide reliable previous data were selected and the cases of MI and sudden death occurring from April 1994 to March 1997 were investigated retrospectively. For all patients, the electrocardiograms recorded before (<1 year) and after the event were obtained and other core data were collected: sex, date of birth, date of onset, date of first medical consultation after the event, dates of admission and discharge, diagnostic information (including cardiac enzyme concentrations), survival at 28 days, previous coronary heart disease, MONICA diagnostic category, and clinical diagnosis. Details of the death, the diagnosis listed on the death certificate, and the findings at autopsy were required in fatal cases.

Background research was also carried out at every collaborating medical center to collect data at 2 times (April 1997 and March 2000). Initial data included the number of employees stratified by sex and age group, smoking rates by sex and age group, rate of annual health screening among workers aged 40 years or older, and the percentage of obese workers (body mass index \( \geq 26.4 \text{ kg/m}^2 \)), as well as the prevalence of hypertension (systolic blood pressure \( \geq 140 \text{ mmHg} \) and/or diastolic blood pressure \( \geq 90 \text{ mmHg} \)), abnormal glucose tolerance (fasting blood glucose \( \geq 110 \text{ mg/dl} \)), and hypercholesterolemia (total cholesterol \( \geq 220 \text{ mg/dl} \)). When the 2nd background study was done, the number of workers per sex and age group was again investigated to detect any changes.

Diagnostic Criteria and Case Fatality Rate

The definitions of coronary events followed the criteria used in the WHO MONICA project. Cases of silent MI and recurrence (a new event occurring more than 28 days after the previous MI) were included. The definition of sudden death was death from an unknown cause within 24 h after the onset of acute symptoms. Death within 28 days after the onset of MI was defined as acute death, and the case fatality rate was the percentage of events that were fatal by 28 days.

All registered cases were reviewed independently by 3 reviewers who were members of the Japanese Circulation Society, and were classified into as fatal or nonfatal (Table 1). In the majority of patients, coronary arteriography and left ventriculography were performed during hospitalization, which we took into account when interpreting the original MONICA criteria. When the assigned category differed among the reviewers, the patient was re-assessed by the review board for final judgment. To allow comparison of our data with the MONICA project and with other Japanese domestic studies, the total number of MI and coronary death events was calculated as \( F_1 + F_2 + F_9 + N F_1 \) (definition 1), \( F_1 + F_2 + N F_1 \) (definition 2), and \( F_1 + F_2 + F_9 + N F_1 + N F_2 \) (definition 3). Therefore, the case fatality rate (percentage) for definition 1 was \( 100 \times \frac{F_1 + F_2 + F_9}{F_1 + F_2 + F_9 + N F_1} \), for definition 2 and \( 100 \times \frac{F_1 + F_2}{F_1 + F_2 + F_9 + N F_1} \), and for definition 3 \( 100 \times \frac{F_1 + F_2 + F_9}{F_1 + F_2 + F_9 + N F_1 + N F_2} \).

Age Standardization and Confidence Intervals (CIs)

Crude annual event rates and case fatality rates were calculated for the study population. Annual event rates and case fatality rates for the subjects aged 35–64 years were adjusted for the age distribution of the World Standard Population by the direct method.
The 95% CIs were calculated by normal approximation of the Poisson distribution.21

### Results

#### Study Sites and Study Population

The 76 participating workplaces are shown in Fig 1. In detail, 1 workplace was on Hokkaido island, 3 were in the Tohoku area, 31 in the Kanto area (including large cities such as Tokyo, Yokohama, Chiba, and Saitama), 7 in the Chubu area, 25 in the Kinki area (including large cities such as Osaka, Kobe, and Kyoto), 5 in the Chugoku-Shikoku area, and 4 in the Kyushu-Okinawa area.

The cities where the workplaces were located showed marked variation in size; for example, 34 workplaces were in 9 major cities with a population of over 1,000,000, 6 workplaces were in 3 cities with a population of more than 500,000 but less than 1,000,000, 24 workplaces were in 19 cities with a population of more than 100,000 but less than 500,000, 3 workplaces were in 3 cities with a population of less than 100,000, and 9 workplaces were in rural areas.

The participating workplaces covered the electrical, automobile, chemical, and machinery industries, as well as finance, insurance, information, communications, trading, and service companies (typical Japanese enterprises). The study populations are shown in Table 2.

#### Background Research

The mean rate of undergoing annual health screening was a high 97.8% among workers aged 40 or older in the study population. The coronary risk factors detected by health screening of the population over 40 years old are shown in Table 3: hypertension (BP ≥140/90 mmHg) in 12.0% of men and 5.6% of women, hypercholesterolemia (total cholesterol ≥220 mg/dl) in 26.5% of men and 25.8% of women, and abnormal glucose tolerance (fasting plasma glucose ≥110 mg/dl) in 11.4% of men and 4.0% of women. Also, the body mass index was ≥26.4 (equivalent to the obesity index +20%) in 11.5% of men and 11.7% of women, and the prevalence of smoking among men was 55.0% in their 40s and 48.7% in their 50s, vs 24.0% and 16.3% for women, respectively.

#### Age and Sex Distribution of Events

The age distribution of the registered events according to sex is shown in Table 4. In men, the total number of fatal

### Table 2 Study Populations

<table>
<thead>
<tr>
<th>Age</th>
<th>≤29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>≥60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>18,713</td>
<td>25,142</td>
<td>35,778</td>
<td>28,993</td>
<td>924</td>
<td>109,550</td>
</tr>
<tr>
<td>Women</td>
<td>11,178</td>
<td>4,499</td>
<td>5,236</td>
<td>2,548</td>
<td>88</td>
<td>23,549</td>
</tr>
<tr>
<td>Total</td>
<td>29,891</td>
<td>29,641</td>
<td>41,014</td>
<td>31,541</td>
<td>1,012</td>
<td>133,099</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>≤29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>≥60</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>37,762</td>
<td>49,680</td>
<td>67,057</td>
<td>51,011</td>
<td>1,800</td>
<td>207,310</td>
</tr>
<tr>
<td>Women</td>
<td>24,731</td>
<td>11,122</td>
<td>9,500</td>
<td>4,619</td>
<td>158</td>
<td>50,130</td>
</tr>
<tr>
<td>Total</td>
<td>62,493</td>
<td>60,802</td>
<td>76,557</td>
<td>55,630</td>
<td>1,958</td>
<td>257,440</td>
</tr>
</tbody>
</table>


### Table 3 Average Incidence of Coronary Risk Factors Among the Subjects Aged ≥40 Years

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (BP ≥140/90 mmHg)</td>
<td>12.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Hypercholesterolemia (total cholesterol ≥220 mg/dl)</td>
<td>26.5</td>
<td>25.8</td>
</tr>
<tr>
<td>Glucose abnormality (fasting plasma glucose ≥110 mg/dl)</td>
<td>11.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Obesity (body mass index ≥26.4 kg/m²)</td>
<td>11.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Cigarette smoking 40–49</td>
<td>55.0</td>
<td>24.0</td>
</tr>
<tr>
<td>50–59</td>
<td>48.7</td>
<td>16.3</td>
</tr>
</tbody>
</table>

*systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Men and women aged 65 years or older were excluded from analysis of the incidence of coronary events and the case fatality rate because of the extremely small sample size for this age group (252 in April 1997 and 278 in March 2000).

### Background Research

The mean rate of undergoing annual health screening was a high 97.8% among workers aged 40 or older in the study population. The coronary risk factors detected by health screening of the population over 40 years old are shown in Table 3: hypertension (BP ≥140/90 mmHg) in 12.0% of men and 5.6% of women, hypercholesterolemia (total cholesterol ≥220 mg/dl) in 26.5% of men and 25.8% of women, and abnormal glucose tolerance (fasting blood glucose ≥110 mg/dl) in 11.4% of men and 4.0% of women. Also, the body mass index was ≥26.4 (equivalent to the obesity index +20%) in 11.5% of men and 11.7% of women, and the prevalence of smoking among men was 55.0% in their 40s and 48.7% in their 50s, vs 24.0% and 16.3% for women, respectively.

### Age and Sex Distribution of Events

The age distribution of the registered events according to sex is shown in Table 4. In men, the total number of fatal...
definite events (F1) was 11 for the age range of 35–64 years, 7 fatal possible events (F2) occurred in the age range of 40–59 years, and 38 fatal unclassifiable events (F9) occurred in the age range of 30–59 years. Also, the total number of nonfatal definite events (NF1) was 218 for the age range of 30–64 years and 19 nonfatal possible events (NF2) occurred in the age range of 40–64 years. The only nonMI case (NF4) was in the age group of 50–54 years. Neither MI nor coronary death was recorded for persons in their 20 s or for those aged 65 years. Among women, a total of 3 cases were registered and all were in their 50 s and were classified as nonfatal definite MI (NF1). Because the number of female cases was so small, subsequent analysis was only performed for men.

**Crude Number of Events and Acute Deaths (Within 28 Days) by Each Definition in Men**

The crude number of events and acute deaths according to each definition are shown in Table 5. The number of events was 274 according to definition 1, 236 according to definition 2, and 293 according to definition 3. The respective number of acute deaths was 56, 18 and 56.

**Crude Annual Event Rates and Case Fatality Rates for Each Age Category in Men**

The crude annual event rates (per 100,000 persons) and case fatality rates according to each definition are shown in Table 6. For definition 1, the crude annual event rate was 0 for men in their 20 s, 2.5 for men aged 30–34 years, 7.6 for men aged 35–39 years, 16.8 for men aged 40–44 years, 49.4 for men aged 45–49 years, 62.1 for men aged 50–54 years, 67.8 for men aged 55–59 years, and 55.6 for men aged 60–64 years. For definition 2, the corresponding rates were 0, 1.7, 2.8, 12.6, 42.2, 58.0, 58.7 and 55.6. For definition 3, they were 0, 2.5, 7.6, 17.7, 52.4, 67.7, 71.9 and 69.5. The crude case fatality rate according to definition 1 was 33.3% at age 30–34 years, 75.0% at 35–39 years, 35.0% at 40–44 years, 20.7% at 45–49 years, 12.2% at 50–54 years, etc.
Table 7  Age-Standardized Annual Event Rates per 100,000 Persons, Case Fatality Rate, Years and Confidence Intervals for Each Definition in Men Aged 35–64

<table>
<thead>
<tr>
<th>Event rate (95% CI)</th>
<th>Case fatality rate (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition 1</td>
<td>40.2 (32.2–48.3)</td>
</tr>
<tr>
<td>Definition 2</td>
<td>35.3 (27.3–43.2)</td>
</tr>
<tr>
<td>Definition 3</td>
<td>44.2 (35.3–53.1)</td>
</tr>
</tbody>
</table>

19.4% at 55–59 years, and 25.0% at 60–64 years. For definition 2, the corresponding rates were 33.3, 13.3, 7.1, 6.0, 6.9 and 2.5. For definition 3, they were 33.3, 75.0, 33.3, 19.5, 11.2, 18.3 and 20.0.

Age-Standardized Annual Event Rates, Case Fatality Rates, and CIs for Each Definition in Men

To compare our results directly with those of the WHO MONICA project and previous Japanese reports, we calculated age-standardized annual event rates, case fatality rates, and CIs for each definition for men aged 35–64 years, based on the World Standard Population and these are shown in Table 7.

Discussion

Participating Workplaces

The workplaces participating in the 3M Study were widely distributed throughout Japan (Fig 1), mostly in urban areas, such as the Kanto or Kinki districts, but many were in medium-sized cities or rural districts, so we considered that they provided a typical picture of Japanese corporations.

Event Rates and Case Fatality Rates Stratified by Age

It is noteworthy that the summary of event rates stratified by age (Table 6) revealed an abrupt increase in MI among men in their late 40s, such as occurs in Western countries and lends support to the age of 45 years or more as an important male coronary risk factor. However, the case fatality rate was actually higher among men in their 30s and early 40s.

The reason for the high case fatality rate in subjects with young-onset MI is not clear at the moment and requires further analyses of coronary risk factors and mental stress in the workplace.

Event Rates and Case Fatality Rates: Comparison With the WHO MONICA Project

According to the WHO MONICA project, the annual event rates for MI and coronary death (definition 1) per 100,000 persons in men aged 35–64 years were 500–800 in Northern Europe and the United Kingdom (regions known to have a high incidence of MI), approximately 500 in the United States, 300–400 in Germany and Italy, and 200–300 in France (which has a relatively low incidence of MI among Western countries). The rate was only 76 in China, as was significantly lower than in Western countries. Compared with these data, the 3M Study found a rate of 40.2 per 100,000 person-years (definition 1) in men, which is extremely low, and the case fatality rate was also very low in this study, being 22.2% compared with 40–55% in Western countries.

Thus, our study revealed extremely low event rates and case fatality rates from MI in male Japanese workers.

Table 8  Annual Health Screening at the Workplace (Legally Required in Japan)

<table>
<thead>
<tr>
<th>1. Weight and height</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Vision and hearing tests</td>
</tr>
<tr>
<td>3. Blood pressure</td>
</tr>
<tr>
<td>4. Urine glucose and protein</td>
</tr>
<tr>
<td>5. Chest X-ray</td>
</tr>
<tr>
<td>6. Electrocardiogram</td>
</tr>
<tr>
<td>7. Blood glucose or hemoglobinA1c</td>
</tr>
<tr>
<td>8. Serum total cholesterol, triglycerides, and HDL-cholesterol</td>
</tr>
<tr>
<td>9. Red blood cell count and hemoglobin</td>
</tr>
<tr>
<td>10. Serum aspartate aminotransferase (AST) alanine aminotransferase (ALT) and γ-glutamyltransferase (γ-GTP)</td>
</tr>
</tbody>
</table>

It may be that these lower coronary event rates in Japan are related to dietary habits, lifestyle, and/or genetic predisposition. According to the Japanese National Nutrition Survey, the ratio of fat intake to total calorie intake first exceeded 20% around 1975, which is 20 years before the start of our study, and has continued to increase gradually up to the current level of 25% or higher. However, fat intake was extremely low (<15%) before 1965. A low intake of fat during the period of physical growth may be one of the major factors contributing to the lower event rates for MI and coronary death in Japan compared with Western countries.

Another relevant factor may be that the Industrial Safety and Health Law of Japan requires all employers to carry out annual health screening of every employee (Table 8) and an occupational physician is also a legal requirement for workplaces with 50 or more workers. Occupational physicians also advise the employer of appropriate health precautions, such as monitoring the job environment transfer of workers, reduction of working hours, and decreasing night shift, as well as providing workers with advice about health and control of coronary risk factors when required. These workplace systems might be an important contributory factor to the low event rates for MI and coronary death among Japanese workers.

Event Rates and Case Fatality Rates: Comparison With Previous Japanese Reports

A population-based study performed in Niigata and Nagaoka cities demonstrated an annual incidence of 80.6 per 100,000 persons for men when data were standardized using the World Standard Population aged 35–64 years for the same definitions of MI and coronary death. According to a 5-year investigation (1990–94) of 9 small to medium workplaces in Osaka, the annual incidence of MI was 72.0 per 100,000 persons among men aged 40–59 years. A report from Okinawa, where mortality from cardiovascular disease is the lowest in Japan, revealed an annual incidence of 53 per 100,000 persons for MI among men aged 35–64 years based on data for 1,200,000 people over 3 years (between 1988 and 1991) adjusted for age using the World Standard Population. Compared with these previously published results, our age-standardized annual incidence of 40.2 per 100,000 persons among men aged 35–64 years (definition 1) was even lower than for Okinawa, probably because our study population was mainly drawn from large workplaces and 97.8% of the workers underwent annual health checks. In medium to small companies and local communities, annual health screening is not as common as the rate shown in this study.

However, Japanese law requires a full-time occupational
physician at workplaces with 1,000 or more workers and a part-time occupational physician at medium-sized workplaces with 50–999 workers. Occupational physicians are not usually assigned to smaller workplaces. At the large workplaces participating in the 3M Study, workers would receive relatively strict management of their coronary risk factors from the medical staff, unlike the smaller companies and local communities for which the current system of medical follow-up may not be sufficient. The percentage of subjects under treatment for hypertension, hyperlipidemia, and diabetes mellitus might have been much higher in this study than in previous reports.

In Japan, most workers are employed soon after graduation from high school or college and remain at the same company until retirement. At the time of employment, employees are so young that it would be difficult to find and exclude persons with CAD or high-risk cases. Whether companies are large or small, the incidence of coronary risk factors from the medical staff, unlike the smaller companies and local communities for which the current system of medical follow-up may not be sufficient. The percentage of subjects under treatment for hypertension, hyperlipidemia, and smoking among young Japanese workers may not be different.

The difference in coronary events should depend on a person’s lifestyle and coronary risk factors in the prime of life. In this respect, a certain positive impact seems to be made by the Japanese system of annual workplace health screening, together with occupational physician systems. Modification of the lifestyle and treatment of coronary risk factors among male workers under the care of occupational physicians is important for the primary prevention of MI and coronary death.

Acknowledgments
This survey could not have been carried out without the cooperation of the participating occupational physicians listed in Appendix 1. We thank them for helping us to obtain the data. We are grateful to Dr. Hirotsugu Ueshima (Shiga University of Medical Science) for his cooperation in conducting the survey and collecting information for this study.

This work was funded by the Japan Association of Occupational Physicians (San-yu-kai) and Banyu Pharmaceutical Co Ltd.

References
Appendix 1

The following persons participated in the 3M Study: