Association of Work Situation With Cardiovascular Disease Mortality Risk Among Working-Age Japanese Men
— A 20-Year Follow-up of NIPPON DATA90 —

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**Background:** Several cohort studies have demonstrated an association between socioeconomic status (SES) and health outcomes in Japan. As long-term employment is common in Japan, the size of the company may be related to cardiovascular disease (CVD) mortality risk. We examined the association of employment conditions with CVD mortality risk among working-age Japanese men (30–59 years, n=2,091).

**Methods and Results:** We used 20-year follow-up data from NIPPON DATA90, for which baseline data were obtained from the 4th National Survey on Circulatory Disorders in 1990. Participants were classified into 4 groups: 3 strata for indefinite-term employees according to company size (large company/public office, moderate-sized, or small), and the self-employed/administrator group. Multivariable-adjusted hazard ratios (HRs) were adjusted for age, lifestyle, and CVD risk factors. Smokers were more common, habitual exercise was less common, and the average systolic blood pressure was higher among indefinite-term employees of small companies compared with employees at large companies/public offices. There was no significant difference in the total CVD mortality risk between indefinite-term employees and self-employed/administrator participants. The age-adjusted HR (95% confidence interval) for total CVD using indefinite-term employees of large companies/public office as a reference was 2.53 (1.12, 5.69) for employees of small companies.

**Conclusions:** Working as an indefinite-term employee at a small company in Japan was significantly associated with elevated risk of CVD mortality among Japanese men.

**Key Words:** Cardiovascular diseases; Cohort studies; Employment; Japanese men; Socioeconomic status

A large number of studies have demonstrated higher rates of cardiovascular disease (CVD) death among individuals of lower socioeconomic status. However, most of those studies are from Western countries, with few from Japan. The average life expectancy in Japan is among the highest in the world, but it was shorter than that in Western developed countries in the 1960s. In addition to changes in individual lifestyles, and progress in treatment of CVD and risk factors, some socioeconomic aspects in Japan may be associated with longevity. Long-term employment has been common in Japan and employ-
ees change their workplace less frequently, which suggests a larger significance of employment on people's lifestyles than in societies in which people change jobs frequently. Working conditions, including salary and working hours, for large-company employees have been better and more stable than those at small companies and may have enabled healthier lifestyles, such as habitual exercise or higher fruit intake. Therefore, the size of the company may be a socioeconomic factor related to CVD mortality risk in Japan.

NIPPON DATA90 is a cohort study based on the 4th National Survey on Circulatory Disorders (NSCD) conducted in Japan in 1990 by the Ministry of Health and Welfare of Japan. The participants were residents from 300 survey districts selected from throughout Japan who also participated in the Comprehensive Survey of Living Conditions (CSLC) and National Nutrition Survey Japan (NNSJ) in the same year. In the present study, we analyzed 20-year follow-up data from NIPPON DATA90 to investigate associations of the working conditions of working-aged Japanese men with mortality risk from CVD.

Methods

A cohort study based on the NSCD in 1990 was named the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trend in the Aged (NIPPON DATA90). We analyzed data from NIPPON DATA90, for which baseline surveys were carried out in 1990, with integration of socioeconomic data obtained from the CSLC in 1990 and results from a dietary survey (NNSJ) in 1990. The details for NIPPON DATA90 have been reported.

Participants in the present study were enrolled in the 3 surveys as follows. In 1990, all households in the 1,040 survey districts randomly selected throughout Japan were enrolled in the CSLC, and data on the living conditions of 152,387 household members from 40,273 households were obtained. From the 1,040 districts, 300 were randomly selected to be enrolled in both the NSCD and NNSJ. Overall, there were 10,959 residents aged ≥30 years in the 300 surveyed districts, and they were invited to participate in the NSCD. A total of 8,383 participants (3,512 men and 4,871 women) agreed to participate (76.5% of the target sample) in the NSCD. The households, including the participants in the NSCD, also enrolled in the NNSJ.

NSCD participants were followed up for survival every 5 years until 2010. In the follow-up surveys, those with incomplete residential information at baseline or those who failed the first follow-up in 1995 were excluded (n=158). Follow-up was made possible through linkage with registration records obtained from municipal governments, with updates that were made available if participants changed residence. We excluded those without a subsequent residential address, which was needed for linkage to necessary statistical records, and finally 8,079 participants (3,405 men; 4,674 women) were able to be followed up.

After verification of data from the 3 surveys (i.e., residential area, sex, age, and family structure), 7,861 participants (3,323 men and 4,538 women) were identified as the same individuals. Detailed procedures for the identification of individual records were previously reported. With permission from the Ministry of Health, Labour and Welfare, we used results from the NSCD, NNSJ, and CSLC. The study was approved by the Institutional Review Board of Shiga University of Medical Science.

Baseline Examinations

The 4th NSCD was conducted on 1 day in November 1990, and consisted of physical examination, blood tests, history taking, and a self-administered questionnaire on lifestyle. The survey was conducted at public health centers according to a standardized manual. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Blood pressure (BP) was measured after a 5-min rest by trained public health nurses using a standard mercury sphygmomanometer. Casual blood samples were obtained. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to 1 laboratory (SRL, Tokyo, Japan). Plasma glucose, serum total cholesterol and triglycerides were measured enzymatically, and high-density lipoprotein cholesterol (HDL-C) was measured by precipitation method using heparin-calcium.

In the questionnaire, participants were asked about their alcohol drinking habit (current, ex-, or never drinker), smoking habit (current, ex-, or never smoker), and awareness of or pharmaceutical treatment for CVD risk factors (hypertension, diabetes mellitus, or dyslipidemia), and history of stroke and coronary artery disease (CAD). Questionnaires were confirmed during face-to-face interviews by trained public health nurses.

National Nutrition Survey Japan (NNSJ)

Three-day semi-weighing dietary records were created for each household enrolled. Trained registered dietitians confirmed the records on the same day as the 4th NSCD was conducted. Food and nutrient intakes per day of each household were calculated using standard food tables, and were proportionally distributed for each household member according to his/her age and sex. Details of the dietary survey and calculation of intake for individual participants have been described previously.

Comprehensive Survey of Living Conditions (CSLC)

Trained interviewers visited each household in the survey district on 1 day in June 1990, and held face-to-face interviews using a questionnaire. During the interviews, participants were asked about the composition of the household, household expenditure in the previous month (May 1990), and the living conditions of each household member such as engagement in employment, health insurance, and public pension. If a participant was employed, he/she was asked to choose one of the following options as the working conditions: self-employed worker who hired ≥1 staff; self-employed worker who did not hire staff; working for a family-owned business; administrator of a company or organization; indefinite-term employee for a company with number of employees of 1–4/5–29/30–99/100–499/500–999/≥1,000 or for a public office; limited-term employee with a term <1 year, homeworker, or other. Self-employment included working in primary industries. Information on the size of company or organization was not collected for administrators.

Endpoint Determination

For the present study, the participants were followed for 20 years until 2010. The procedure used to determine the endpoint in our study has been previously reported. Briefly,
Statistical Analysis
In order to investigate associations of working conditions with CVD death, we used data for men aged 30–59 years (n=2,256) because the age of retirement was set at 60 years for indefinite-term employees at most workplaces in Japan, and information on former working conditions of retired persons was not collected in the CSLC. Among the men, participants with a past history of stroke or CAD were excluded (n=56), as were subjects with missing data on BMI, smoking and drinking habits, history of stroke or CAD, or other variables necessary for the analysis (n=21). We also excluded limited-term employees (n=27) and unemployed subjects (n=61) because they may not have been engaged in continuous work due to their poor health, which was considered inappropriate in the present analyses on work and disease relationship. The remaining sample used in this report comprised 2,091 male participants. We did not include female participants because many of them of similar age were not employed (41.2%, data not shown) and there were fewer indefinite-term employees (28.6%); therefore, we considered them unsuitable for the present analyses.

Participants were categorized into 4 strata according to their working conditions and dummy variables were created: indefinite-term employees for large companies (≥500 employees) or public offices, medium companies (30–499 employees), small companies (1–29 employees), and self-employed individuals, including those working for family businesses or administrators. We combined large-company employees (n=357) and public officials (n=245) into the same stratum because the average wage level of public officials is similar to that of large-company employees. Furthermore, employment has been generally stable at large companies and public officials are guaranteed stable employment. We also combined self-employed individuals (n=569) and administrators (n=115) because they both may have been engaged in diverse working conditions and may have been given more discretion in their work than employees.

Comparisons were made between indefinite-term employees and the self-employed/administrator group, and among the 3 strata of indefinite-term employees according to company size. Differences in baseline characteristics across the strata were compared by t-tests or analysis of variance for continuous variables, or chi-squared test for categorical variables. Age-adjusted mortality was calculated by the continuous variables, or chi-squared test for categorical variables. Age-adjusted mortality was calculated by the direct method using the Japanese model population in 1985 for each group. To examine the association of working conditions with mortality endpoints, Cox proportional hazards models were used. Hazard ratios (HRs) for the self-employed/administrator group in reference to indefinite-term employees, and for indefinite-term employees of medium or small companies in reference to those of large companies/public offices were obtained. Three models were examined: Model 1 included age (year) as a covariate; Model 2 included additional covariates: BMI (kg/m²), smoking (current, ex-, or never smoker [reference]) and drinking (current, ex-, or never drinker [reference]) behaviors, salt intake (g/1,000 kcal), and fruit and vegetable intake (g/1,000 kcal); Model 3 included further adjustments made for the population size of the residential municipality (<200,000 [reference] or ≥200,000) as an index of rural or urban area, the use of medication (yes or no [reference]) for hypertension, diabetes mellitus, or dyslipidemia, and level of risk factors: systolic BP (mmHg), diastolic BP (mmHg), HbA1c (%), serum total cholesterol (mg/dL), HDL-C (mg/dL), and triglycerides (mg/dL). Adjusted probability of freedom from death was calculated with mean of covariates by multivariable Cox proportional hazards model analysis (Model 3).

Hypothesis testing was two-sided with a significance level of 0.05. SPSS v.22.0 for Windows (IBM Corporation, Tokyo, Japan) was used for all analyses.

Results
Baseline characteristics of participants are shown in Table 1. On comparison of indefinite-term employees and the self-employed/administrator group, indefinite-term employees were younger. Habitual exercise was more common among indefinite-term employees (20.8%) than among self-employed/administrator participants (15.8%). Self-employed/administrator participants consumed more vegetables, salt, and potassium. The average BP level and percentage of those receiving antihypertensive drugs were higher among self-employed/administrator participants than among indefinite-term employees.

Based on comparisons among the 3 strata of indefinite-term employees according to company size, unhealthy lifestyles were more common among small-company employees than large-company/public office employees; there was a higher percentage of current smokers (63.8%) of small-company employees vs. 53.5% of large-company/public office employees) and less habitual exercise (18.6% vs. 25.7%). They consumed less fruit and potassium, and the dietary Na/K ratio was higher than that of large-company/public office employees. Although the average systolic BP was higher for small-company employees than for large-company/public office employees (133.0 mmHg vs. 130.5 mmHg), awareness of hypertension was lower among small-company employees than among large-company/public office employees (12.6% vs. 15.8%).

In total, 39,433 person-years were studied during the 20-year follow-up. The age-adjusted mortality rates per 100,000 person-years according to working conditions are shown in Table 2. The age-adjusted total CVD mortality rate for the self-employed/administrator group was similar to that for indefinite-term employees. Among the indefinite-term employees, the adjusted mortality rates for total CVD were higher for those working at small companies than for those at medium or large companies/public offices; the rate was 92, 135, and 222 for employees at large companies/public offices, medium companies, and small companies, respectively. For all-cause death, the difference in mortality rate among the strata was smaller; the respective rates for the 3 strata were 457, 586, and 594.

Results from the Cox analyses on the association of working conditions with the risk of total CVD and all-cause mortality are shown in Table 3 and Table 4. There was no significant difference in the risk of total CVD or all-cause death between indefinite-term employees and the
self-employed/administrator group (Table 3). Analyses among the indefinite-term employee strata according to company size (Table 4) demonstrated a significantly higher mortality risk from total CVD for small-company employees than for large-company/public office employees. The age-adjusted HR (95% confidence interval [CI]) in Model 1 was 2.53 (1.12, 5.70), and it was similar and significant after further adjustments for lifestyle factors and CVD risk factors: 2.54 (1.12, 5.76) with Model 2 and 2.85 (1.16, 7.04) with Model 3. There was no significant difference in the all-cause mortality risk among the 3 strata of indefinite-term employees.

The probability of freedom from death among the working conditions based on the multivariable Cox hazards model using the mean of covariates for Model 3 is shown in Figure. The adjusted probability at 20 years of follow-up was as follows: indefinite-term employees for large company/public office, 98.6%; medium company, 97.2%; small company, 95.7%; and self-employed/administrator group, 97.0%.
between indefinite-term employees and the self-employed/administrator group, working for a small company as an indefinite-term employee was associated with a significantly increased risk of death from CVD compared with large-company or public office employees. To the best of our knowledge, this is the first study to demonstrate asso-

Discussion

We examined the association between CVD mortality risk and working conditions using 20-year follow-up data from 1990 of a cohort of working-age Japanese males. Although there was no significant difference in the mortality risk between indefinite-term employees and the self-employed/administrator group, working for a small company as an indefinite-term employee was associated with a significantly increased risk of death from CVD compared with large-company or public office employees. To the best of our knowledge, this is the first study to demonstrate asso-

| Person-years | Indefinite-term employees | Total | Large company/public office | Medium company | All indefinite-term employees | Self-employed/administrator |
|--------------|---------------------------|-------|-----------------------------|---------------|-----------------------------|-----------------------------|
| No. of deaths (age-adjusted mortality rate*) | | | | | | |
| Total CVD | 61 | 10 (92) | 12 (135) | 14 (222) | 36 (135) | 25 (144) |
| All-cause | 225 | 51 (457) | 54 (586) | 36 (594) | 141 (531) | 84 (504) |

*Person-year mortality rate per 100,000 person-years, adjusted for age using the Japanese model population in 1985. CVD, cardiovascular disease.

| Table 2. Person-Years, Number of Deaths, and Age-Adjusted Mortality Rates From CVD: 20-Year Follow-up of 2091 Japanese Men Aged 30–59 Years (NIPPON DATA90 Study) |
|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Person-years | Indefinite-term employees | Total | Large company/public office | Medium company | All indefinite-term employees | Self-employed/administrator |
| No. of deaths (age-adjusted mortality rate*) | | | | | | |
| Total CVD | 61 | 10 (92) | 12 (135) | 14 (222) | 36 (135) | 25 (144) |
| All-cause | 225 | 51 (457) | 54 (586) | 36 (594) | 141 (531) | 84 (504) |

Model 1: adjusted for age. Model 2: further adjusted for BMI (kg/m²), smoking habit (current, ex-, or never), drinking habit (current, ex-, or never), salt intake (g(1,000 kcal), and fruit and vegetable intake (g/1,000 kcal). Model 3: adjusted for factors in Model 2, population size of the residential municipality (<200,000 or ≥200,000), and use of medications for hypertension, diabetes mellitus, or dyslipidemia, SBP (mmHg), DBP (mmHg), HbA1c (%), serum TC (mg/dL), HDL-C (mg/dL), and TG (mg/dL). CI, confidence intervals; HRs, hazard ratios. Other abbreviations as in Table 1.

| Table 3. Multivariable-Adjusted HRs and 95% CI for Total CVD and All-Cause Mortality Among Indefinite-Term Employees and Self-Employed/Administrator Participants: 20-Year Follow-up of Japanese Men Aged 30–59 Years (NIPPON DATA90 Study) |
|------------------------------------|------------------------------------|------------------------------------|
| All indefinite-term employees | Self-employed/administrator | HR (95% CI) | P value |
| Total CVD mortality | | 1 | 1.13 (0.68–1.89) | 0.642 |
| Model 1 | 1 | 1.06 (0.63–1.78) | 0.839 |
| Model 2 | 1 | 0.94 (0.54–1.63) | 0.824 |
| All-cause mortality | | 1 | 0.96 (0.73–1.26) | 0.780 |
| Model 1 | 1 | 0.94 (0.71–1.24) | 0.646 |
| Model 2 | 1 | 1.20 (0.67–2.02) | 0.471 |

Model 1: adjusted for age. Model 2: further adjusted for BMI (kg/m²), smoking habit (current, ex-, or never), drinking habit (current, ex-, or never), salt intake (g/1,000 kcal), and fruit and vegetable intake (g/1,000 kcal). Model 3: adjusted for factors in Model 2, population size of the residential municipality (<200,000 or ≥200,000), and use of medications for hypertension, diabetes mellitus, or dyslipidemia, SBP (mmHg), DBP (mmHg), HbA1c (%), serum TC (mg/dL), HDL-C (mg/dL), and TG (mg/dL). CI, confidence intervals; HRs, hazard ratios. Other abbreviations as in Table 1.

| Table 4. Multivariable-Adjusted HR and 95% CI for Total CVD and All-Cause Mortality Among Indefinite-Term Employees According to Company Size: 20-Year Follow-up of Japanese Men Aged 30–59 Years (NIPPON DATA90 Study) |
|------------------------------------|------------------------------------|------------------------------------|
| Total CVD mortality | | | |
| Large company/public office | Medium company | Small company |
| HR (95% CI) | P value | HR (95% CI) | P value |
| Model 1 | 1 | 1.44 (0.62–3.35) | 0.392 | 2.53 (1.12–5.70) | 0.025 |
| Model 2 | 1 | 1.39 (0.59–3.25) | 0.450 | 2.54 (1.12–5.76) | 0.026 |
| Model 3 | 1 | 1.68 (0.67–4.23) | 0.272 | 2.85 (1.16–7.04) | 0.023 |
| All-cause mortality | | | |
| Model 1 | 1 | 1.26 (0.86–1.84) | 0.245 | 1.27 (0.83–1.94) | 0.275 |
| Model 2 | 1 | 1.20 (0.81–1.77) | 0.365 | 1.26 (0.82–1.94) | 0.300 |
| Model 3 | 1 | 1.25 (0.83–1.88) | 0.289 | 1.29 (0.82–2.02) | 0.270 |

Model 1: adjusted for age. Model 2: further adjusted for BMI (kg/m²), smoking habit (current, ex-, or never), drinking habit (current, ex-, or never), salt intake (g/1,000 kcal), and fruit and vegetable intake (g/1,000 kcal). Model 3: adjusted for factors in Model 2, population size of the residential municipality (<200,000 or ≥200,000), and use of medications for hypertension, diabetes mellitus, or dyslipidemia, SBP (mmHg), DBP (mmHg), HbA1c (%), serum TC (mg/dL), HDL-C (mg/dL), and TG (mg/dL). CI, confidence intervals; HRs, hazard ratios. Other abbreviations as in Tables 1, 3.
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insurance (70.7%), followed by government-managed health insurance (35.4%) and citizen’s health insurance (26.5%).

The lower awareness and rate of pharmaceutical treatment for CVD risk factors observed for small-company employees as compared with large-company/public office employees may have been because of lower participation in checkups. Lack of awareness of elevated BP, blood glucose, and/or dyslipidemia may lead to missed opportunities to receive medical care or improve lifestyle to prevent CVD events.

The Industry Safety and Health Act in Japan requires employers to assign occupational physicians to full-time assignments for workplaces with ≥500 employees or part-time assignments for workplaces with 50–499 employees. These physicians engage in primary prevention of non-communicable diseases, including CVD, at the workplace.

In the multivariable Cox proportional hazards model analyses, additional adjustments for lifestyle factors or CVD risk factors did not significantly alter the associations of working conditions with the risk of CVD death. There is a possibility that it was more difficult for small-company employees to receive satisfactory treatment even after diagnosis, both non-pharmaceutical and pharmaceutical, than large-company employees. Furthermore, it may have been difficult to have a healthier diet, such as increased intake of vegetables and fruits, because of lower wages. Average labor hours have been reported to be longer for small-company employees than for large-company employees, which may have made it difficult for the small-company employees to exercise or to visit clinics regularly to get prescriptions. Before 2002, physicians were not allowed to pre-

Figure. Probability of freedom from total CVD death (A) and all-cause death (B) according to working conditions by multivariable Cox proportional hazard model analysis with means of covariates. A 20-year follow-up of 2,091 Japanese men aged 30–59 years. NIPPON DATA90 Study. Adjusted variables were age, body mass index (kg/m²), smoking habit (current-, ex-, never), drinking habit (current, ex-, and never), salt intake (g/1,000 kcal), fruit and vegetable intake (g/1,000 kcal), population size of residential municipality (<200,000 or ≥200,000), use of medications for hypertension, diabetes mellitus, dyslipidemia, systolic blood pressure (mmHg), diastolic blood pressure (mmHg), HbA1c (%), serum total cholesterol (mg/dL), high-density lipoprotein cholesterol (mg/dL), and triglycerides (mg/dL). CVD, cardiovascular disease.
scribe medication for longer than 30 days according to the Medical Service Act, even for stable patients with chronic disease, and patients had to visit the clinic monthly. Furthermore, there may have been unknown confounding factors that were not adjusted for.

There was no significant difference in the CVD mortality risk between indefinite-term employees and self-employed/administrator participants. Self-employed persons may have engaged in diverse employment conditions such as income level or type of work. Administrators may also have worked for various companies of diverse size in different industries, which may have affected their income levels and other working conditions. These reasons may account for the lack of difference between self-employed/administrator participants and indefinite-term employees.

Regarding the all-cause mortality risk, we did not observe a significant increase in HR for small-company employees even though they had a significant CVD mortality risk. In the present dataset, CVD deaths accounted for 27% of the total deaths. Since the 1980s, the leading cause of death in Japan has been cancer, and the cancer mortality rate has been greater than that of CVD in recent years. Although studies on the association between SES and cancer mortality in Japan are scarce, there was no significant association between education level and all-cancer mortality risk in the multivariable-adjusted analysis in a recent cohort study. CVD may be a disease for which healthcare activity in accordance with working conditions is effective.

Study Limitations

First, data on working conditions were obtained only once in 1990, and participants may have changed their jobs or workplaces afterward. This may have attenuated the true relationship between working conditions and CVD death. Second, the educational and income levels of participants were not considered in the analysis because of the lack of information. Moreover, the subjects of the present study participated in 3 previous surveys, the CSLC, NHNSJ, and NSCD, which included a dietary survey, physical measurements, and blood tests. The participants may have participated actively in other health-related activities, including workplace health checkups and medical treatment of diseases. Thus, the possibility of a selection bias cannot be excluded. Limited-term employees and unemployed participants were excluded from the analysis, and we did not examine these associations for women.

Conclusions

Working for small companies as an indefinite-term male employee was found to be associated with unfavorable lifestyles and increased mortality risk from CVD compared with working for large companies/public office. The association did not change after adjusting for lifestyle factors or treatment of risk factors. It may be difficult for small company employees to take appropriate action to prevent and treat CVD.

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