## Discussion

Our study presented the risk of q wave abnormality by grade of MC for CVD mortality and its subtypes among Japanese general population who are free from CVD history. Although the prevalence of moderate and severe q wave abnormality was low (0.4%), the significant increase of HRs was observed among the participants with moderate and severe q wave abnormality for heart disease mortality. The HRs of moderate and severe q wave abnormality for mortality from CVD and heart disease were also significantly elevated when the participants with ST, T wave abnormality and high amplitude R waves were excluded. Furthermore, when the participants were divided into the subgroups according to the presence of hypertension, hyperglycemia, and hyperlipidemia, the HRs of moderate and severe q wave abnormality for mortality due to CVD and heart disease were also consistently elevated. Q wave abnormality was not associated with the risk of stroke mortality.

Previous studies reported that major q wave abnormality (MC, 1-1) predict all cause and CVD mortality [2]. However, few studies reported the risk of q wave abnormality by grade. Rose et al reported that age-adjusted coronary heart disease mortality became higher according to the grade of q waves in their five-year follow-up study [5], but they did not assess the multivariate- adjusted HR of q wave abnormality.

Our study is the first report which presented the risk of q wave by grade independent from both ECG abnormalities such as ST-T abnormality and high amplitude R waves and other CVD risk factors. Previous study reported that even minor ST-T abnormalities were associated with increased long-term risk of mortality or incidence due to stroke, CHD, and CVD [3, 26]. As we reported previously, high left R waves are associated with CVD mortality[25]. Accordingly, we excluded the participants with ST - T wave abnormality and high amplitude R waves to assess the risk of q wave abnormality independent from other ECG abnormalities. The participants with moderate or severe q wave abnormality showed the significant increase of HR for CVD and heart disease even when ST - T wave abnormality and high amplitude R waves were excluded. People in the community with MC 1-1 and MC 1-2 are considered to be high risk group for death due to CVD or heart diseases regardless of ST-T change and high R waves, and should be under search for determining specific etiologies.

The risk of the q wave abnormality was assessed according to the presence of three major CVD risk factors. Essentially, moderate or severe q wave abnormalities were associated with the risk of mortality due to CVD or heart diseases regardless of the presence of three major CVD risk factors. Vast majority of abnormal q waves are due to myocardial infarction, but a significant numbers are due to other causes such as cardiomyopathy, chronic obstructive lung disease[4] and found in patients with nephropathy[27]. ECG screening is a simple, inexpensive and widely available test compared to the various kinds of specific tests to screen people with those diseases in communities. Moreover, ECG is able to increase the predictive value for identifying individuals at high-risk for CVD and heart disease mortality in addition to classic CVD risk factors.

The participants of this study were from a nationwide cohort study, and they were selected by a stratified random sampling method. Accordingly, the results of the present study would apply to the general Japanese population. Furthermore, the participants in our study were observed for 19 years, which is a long follow-up period and increases the value of our study substantially.

One of the limitations of our study is that the number of the participants with q wave abnormality was small. Accordingly, we could not divide the participants into three q wave categories (MC, 1-1, 1-2, and1-3) and assess the risk of q wave abnormality according to the subtypes of stroke or heart diseases respectively. And we could not investigate the prognostic value of mild q wave abnormality sufficiently in this study. Secondly, MC was coded by visual reading in our study. Computerized ECG analysis is reported that it appears superior to visual reading to better reliability [28]. However, ECG reading of this study was performed under the best standardized quality control in 1980. Third, we could not assess the risk of q wave abnormalities according to the lead in which q waves existed to evaluate their clinical meanings because there is no data concerning about the lead at the baseline survey.

In conclusion, moderate or severe q wave abnormality is associated with elevated risk for mortality from CVD or heart diseases independent from other ECG changes among the participants with no CVD history. Although the prevalence of q wave abnormality is not high among the participants without history of CVD in communities, q wave abnormality is prominent and important predictor for CVD and heart disease mortality.

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## Appendix

**List of the NIPPON DATA80 Research Group**

**NIPPON DATA80:** "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged"

Chair man: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga)

**Consultant:** Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Horibe (Aichi Medical University , Nagakute, Aichi)

**Research Member:** Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Chiyoda-ku, Tokyo), Kazunori Kodama, Fumiyoshi Kasagi (Radiation Effects Research Foundation, Hiroshima, Hiroshima), Tomonori Okamura (Department of Preventive Cardiology, National Cardiovascular Center, Suita, Osaka), Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Fukushima), Shinichi Tanihara (Department of Public Health, School of Medicine, Shimane University, Izumo, Shimane), Shigeyuki Saitoh (Second Department of Internal Medicine School of Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University School of Medicine, Morioka, Iwate), Yosikazu Nakamura (Department of Health Science Division of Epidemiology and Community Health, Jichi Medical School, Minami Kawachi, Tochigi), Fumihiko Kakuno (Hikone Public Health Center, Hikone, Shiga)

**Research Associate Member:** Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Sohel R. Choudhury (National Heart Foundation Hospital & Research Institute, Dhaka, Bangladesh), Yutaka Kiyohara (Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Fukuoka), Minoru Iida (Kansai University of Welfare Sciences, Kashihara, Kashiwara Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama)

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**Table 1. Definition of cause of death (ICD 9 or ICD10 †codes )**

| Causes of Death | ICD 9code (-1994) | ICD 10code (1995-) |
|---|---|---|
| Chronic rheumatic heart disease | 393-398 | I05-I09 |
| Hypertensive disease | 401-405 | I10-I15 |
| Ischemic heart disease | 410-414 | I20-I25 |
| Diseases of pulmonary circulation | 415-417 | I26-I28 |
| Other forms of heart disease | 420-429 | I30-I52 |
| Cerebrovascular disease | 430-438 | I60-I69 |
| Diseases of arteries, arterioles, and capilla | 440-448 | I70-I79 |
| Diseases of vein and lymphatics, and other diseases of circulatory system | 451-459 | I80-I99 |

† ICD 9 and ICD 10 means the 9th or 10th International Classification of Diseas

**Table 2.Baseline characteristics of the participants according to the q wave abnormality : NIPPON DATA80, 1980-1999, Japan**

| | normal | q wave mild (1-3-) | moderate or severe (1-1-)+(1-2-) | p |
|---|---|---|---|---|
| **Men** | | | | |
| N | 3609 | 62 | 23 | |
| Age (years) † | 50 ± 13 | 54 ± 14 | 59 ± 17 | <0.001 |
| Body mass index (kg/m$^2$) † | 22.5 ± 2.8 | 22.9 ± 3.1 | 22.1 ± 3.1 | 0.500 |
| History of diabetes mellitus (%)‡ | 4.0 | 9.7 | 0.0 | <0.05 |
| Systolic blood pressure (mmHg) † | 138 ± 20 | 141 ± 21 | 150 ± 28 | <0.01 |
| Diastolic blood pressure (mmHg) † | 84 ± 12 | 83 ± 13 | 85 ± 14 | 0.82 |
| Hypertension (%) ‡ | 48.9 | 61.3 | 69.6 | <0.05 |
| Medication for hypertension (%) ‡ | 8.8 | 21.0 | 17.4 | <0.01 |
| Serum total cholesterol (mg/dl) † | 187 ± 33 | 194 ± 33 | 203 ± 62 | <0.05 |
| Hyperlipidemia (%) ‡ | 31.4 | 40.3 | 39.1 | 0.24 |
| Glucose (mg/dl) † | 101 ± 33 | 103 ± 27 | 116 ± 41 | 0.08 |
| Hyperglycemia (%) ‡ | 9.2 | 17.7 | 21.7 | <0.05 |
| Smoking (%)‡ | 63.4 | 66.1 | 69.6 | 0.76 |
| Alcohol drinking (%)‡ | 75.3 | 74.2 | 56.5 | 0.12 |
| **Women** | | | | |
| N | 4586 | 46 | 13 | |
| Age (years) † | 50 ± 13 | 57 ± 14 | 65 ± 13 | <0.001 |
| Body mass index (kg/m$^2$) † | 22.8 ± 3.3 | 23 ± 4 | 24.4 ± 4.6 | 0.22 |
| History of diabetes mellitus (%)‡ | 2.0 | 2.2 | 15.4 | <0.01 |
| Systolic blood pressure (mmHg) † | 133 ± 21 | 139 ± 21 | 142 ± 33 | 0.05 |
| Diastolic blood pressure (mmHg) † | 79 ± 12 | 82 ± 11 | 84 ± 17 | 0.12 |
| Hypertension (%) ‡ | 39.6 | 50.0 | 53.8 | 0.21 |
| Medication for hypertension (%) ‡ | 37.3 | 45.7 | 53.8 | 0.24 |
| Serum total cholesterol (mg/dl) † | 190 ± 34 | 199 ± 34 | 202 ± 50 | 0.09 |
| Hyperlipidemia (%) ‡ | 36.0 | 43.5 | 46.2 | 0.44 |
| Glucose (mg/dl) † | 99 ± 28 | 116 ± 78 | 128 ± 58 | <0.01 |
| Hyperglycemia (%) ‡ | 5.7 | 8.7 | 23.1 | <0.05 |
| Smoking (%)‡ | 8.7 | 15.2 | 0.0 | 0.16 |
| Alcohol drinking (%)‡ | 20.3 | 8.7 | 30.8 | 0.10 |

Values located after the mark, ±, indicate standard deviation. † analysis of variance. ‡ chi-square test.
(1-3-) or (1-1-)+(1-2-) indicates ECG codes classified by Minnesota Codes.
Hypertension; systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current medication for hypertension.
Hyperlipidemia; total cholesterol ≥ 200 mg/dl.
Hyperglycemia; glucose ≥ 140 mg/dl and/or the presence of history of diabetes mellitus .

**Table3. Risk of q wave abnormality for CVD mortality and its subtypes: NIPPON DATA80, 1980-1999, Japan**

| | CVD | | | Stroke | | | Heart Diseases | | |
|---|---|---|---|---|---|---|---|---|---|
| | | q wave | | | q wave | | | q wave | |
| | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) |
| **Men** | | | | | | | | | |
| N | 3609 | 62 | 23 | 3609 | 62 | 23 | 3609 | 62 | 23 |
| Person-years of follow-up | 61733 | 966 | 284 | 61752 | 966 | 284 | 61752 | 966 | 284 |
| Case | 263 | 7 | 9 | 136 | 1 | 2 | 115 | 5 | 6 |
| Mortality (/1000 person-years) | 4.26 | 7.25 | 31.73 | 2.20 | 1.04 | 7.05 | 1.86 | 5.18 | 21.16 |
| Age-adjusted hazard ratios | 1.00 | 1.23 (0.58-2.61) | 3.34 (1.71-6.53) * | 1.00 | 0.33 (0.05-2.38) | 1.32 (0.33-5.38) | 1.00 | 2.06 (0.84-5.05) | 5.51 (2.40-12.64) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.27 (0.60-2.71) | 1.79 (0.87-3.65) | 1.00 | 0.36 (0.05-2.60) | 0.74 (0.17-3.16) | 1.00 | 2.02 (0.82-4.98) | 2.93 (1.20-7.15) * |
| **Women** | | | | | | | | | |
| N | 4586 | 46 | 13 | 4586 | 46 | 13 | 4587 | 46 | 13 |
| Person-years of follow-up | 81187 | 736 | 194 | 81206 | 736 | 194 | 81206 | 736 | 194 |
| Case | 254 | 8 | 3 | 114 | 4 | 0 | 125 | 4 | 2 |
| Mortality (/1000 person-years) | 3.13 | 10.87 | 15.44 | 1.40 | 5.44 | – | 1.54 | 5.44 | 10.29 |
| Age-adjusted hazard ratios | 1.00 | 1.86 (0.92-3.77) | 1.70 (0.54-5.30) | 1.00 | 2.10 (0.77-5.71) | – | 1.00 | 1.92 (0.71-5.21) | 2.29 (0.57-9.28) |
| Multivariate-adjusted hazard ratios | 1.00 | 1.87 (0.92-3.80) | 1.69 (0.54-5.29) | 1.00 | 2.06 (0.75-5.62) | – | 1.00 | 2.02 (0.74-5.50) | 2.38 (0.59-9.70) |
| **Men and Women** | | | | | | | | | |
| N | 8195 | 108 | 36 | 8195 | 108 | 36 | 8197 | 108 | 36 |
| Person-years of follow-up | 142920 | 1702 | 478 | 142958 | 1702 | 478 | 142958 | 1702 | 478 |
| Case | 517 | 15 | 12 | 250 | 5 | 2 | 240 | 9 | 8 |
| Mortality (/1000 person-years) | 3.62 | 8.81 | 25.11 | 1.75 | 2.94 | 4.19 | 1.68 | 5.29 | 16.74 |
| Age-adjusted hazard ratios | 1.00 | 1.49 (0.89-2.50) | 2.61 (1.47-4.65) * | 1.00 | 1.00 (0.41-2.44) | 0.86 (0.21-3.46) | 1.00 | 1.99 (1.02-3.88) * | 3.96 (1.95-8.03) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.50 (0.90-2.51) | 1.75 (0.97-3.17) | 1.00 | 1.05 (0.43-2.56) | 0.48 (0.12-2.00) | 1.00 | 1.95 (1.00-3.81) * | 2.97 (1.43-6.16) * |

Values in parentheses indicate 95% confidence interval of hazard ratios. The mark, *, indicates statisitically significant difference compared to the reference.
The age-adjusted hazard ratio: the grade of the q wave abnormality and age at study entry were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
The multivariate-adjusted hazard ratio: the grade of the q wave abnormality, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol drinking, and the presence of hyperglycemia (glucose ≥ 140 mg/dl and/or the presence of history of diabetes mellitus) were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
(1-3-) or (1-1-)+(1-2-) indicates ECG codes classified by Minnesota Codes.

**Table 4. Risk of q wave abnormality for CVD mortality and its subtypes when the participants with ST depression, T wave abnormality, and high amplitude R waves were excluded: NIPPON DATA80, 1980-1999, Japan**

| | CVD | | | Stroke | | | Heart Diseases | | |
|---|---|---|---|---|---|---|---|---|---|
| | | q wave | | | q wave | | | q wave | |
| | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) |
| **ST depression and T wave abnormality excluded** | | | | | | | | | |
| N | 7389 | 86 | 19 | 7389 | 86 | 19 | 7389 | 86 | 19 |
| Person-years of follow-up | 130072 | 1425 | 258 | 130072 | 1425 | 258 | 130072 | 1425 | 258 |
| Case | 393 | 8 | 6 | 192 | 3 | 2 | 180 | 5 | 3 |
| Mortality (/1000 person-years) | 3.02 | 5.62 | 23.24 | 1.48 | 2.11 | 7.75 | 1.38 | 3.51 | 11.62 |
| Age-adjusted hazard ratios | 1.00 | 1.13 (0.56-2.27) | 8.12 (3.61-18.22) * | 1.00 | 0.84 (0.27-2.63) | 5.39 (1.33-21.78) * | 1.00 | 1.58 (0.65-3.86) | 8.98 (2.86-28.21) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.20 (0.60-2.43) | 5.33 (2.33-12.21) * | 1.00 | 0.93 (0.30-2.91) | 3.56 (0.86-14.80) | 1.00 | 1.66 (0.68-4.05) | 6.14 (1.91-19.78) * |
| **ST depression, T wave abnormality and high amplitude R wave excluded** | | | | | | | | | |
| N | 6350 | 73 | 14 | 6350 | 73 | 14 | 6350 | 73 | 14 |
| Person-years of follow-up | 112095 | 1191 | 197 | 112095 | 1191 | 197 | 112095 | 1191 | 197 |
| Case | 320 | 7 | 3 | 150 | 2 | 1 | 153 | 5 | 2 |
| Mortality (/1000 person-years) | 2.85 | 5.88 | 15.23 | 1.34 | 1.68 | 5.08 | 1.36 | 4.20 | 10.15 |
| Age-adjusted hazard ratios | 1.00 | 1.15 (0.54-2.44) | 7.11 (2.28-22.25) * | 1.00 | 0.67 (0.17-2.71) | 5.04 (0.70-36.20) | 1.00 | 1.75 (0.72-4.30) | 10.01 (2.47-40.56) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.21 (0.57-2.57) | 4.46 (1.39-14.32) * | 1.00 | 0.72 (0.18-2.93) | 2.89 (0.39-21.61) | 1.00 | 1.82 (0.74-4.47) | 6.83 (1.63-28.57) * |

Values in parentheses indicate 95% confidence interval of hazard ratios. The mark, *, indicates statisitically significant difference compared to the reference.
The age-adjusted hazard ratio: the grade of q wave abnormality, sex, and age at study entry were entered in the model.
The multivariate-adjusted hazard ratio: the grade of q wave abnormality, sex, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking, alcohol drinking, and the presence of hyperglycemia (glucose ≥ 140 mg/dl and/or the presence of history of diabetes mellitus) were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.
(1-3-) or (1-1-)+(1-2-) indicates ECG codes classified by Minnesota Codes (MS).
ST depression: MC 4-1 ~ 4-4. T wave abnormality: MC 5-1 ~ 5-4. high amplitude R waves: MC 3-1 ~ 3-4.

**Table 5. Risk of q wave abnormality according to the presence of hypertension, hyperglycemia, and hyperlipidemia: NIPPON DATA80, 1980-1999, Japan**

| | CVD | | | Heart Diseases | | |
|---|---|---|---|---|---|---|
| | | q wave | | | q wave | |
| | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) | normal | mild (1-3-) | moderate or severe (1-1-)+(1-2-) |
| Hypertension (-) (N:4671) | | | | | | |
| N | 4611 | 47 | 13 | 4611 | 47 | 13 |
| Person-years of follow-up | 83232 | 847 | 192 | 83232 | 847 | 192 |
| Case | 123 | 4 | 3 | 69 | 3 | 2 |
| Mortality (/1000 person-years) | 1.48 | 4.72 | 15.63 | 0.83 | 3.54 | 10.42 |
| Age-adjusted hazard ratios | 1.00 | 2.23 (0.82-6.04) | 5.06 (1.59-16.14) * | 1.00 | 2.97 (0.93-9.46) | 5.58 (1.34-23.20) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.76 (0.64-4.82) | 4.99 (1.56-15.95) * | 1.00 | 2.25 (0.70-7.28) | 5.62 (1.34-23.50) * |
| Hypertension (+) (N:3668) | | | | | | |
| N | 3584 | 61 | 23 | 3584 | 61 | 23 |
| Person-years of follow-up | 59688 | 855 | 286 | 59688 | 855 | 286 |
| Case | 394 | 11 | 9 | 171 | 6 | 6 |
| Mortality (/1000 person-years) | 6.60 | 12.86 | 31.48 | 2.86 | 7.02 | 20.99 |
| Age-adjusted hazard ratios | 1.00 | 1.35 (0.74-2.45) | 2.17 (1.12-4.21) * | 1.00 | 1.77 (0.78-4.01) | 3.52 (1.55-7.98) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.38 (0.75-2.52) | 1.59 (0.80-3.17) | 1.00 | 1.81(0.86-4.12) | 2.74 (1.17-6.41) * |
| Hyperglycemia (-) (N:6283) | | | | | | |
| N | 6194 | 69 | 20 | 6194 | 69 | 20 |
| Person-years of follow-up | 109575 | 1186 | 292 | 109575 | 1186 | 292 |
| Case | 297 | 7 | 8 | 141 | 3 | 5 |
| Mortality (/1000 person-years) | 2.71 | 5.90 | 27.40 | 1.29 | 2.53 | 17.12 |
| Age-adjusted hazard ratios | 1.00 | 1.72 (0.81-3.64) | 3.37 (1.66-6.85) * | 1.00 | 1.54 (0.49-4.83) | 4.46 (1.81-10.99) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.59 (0.75-3.37) | 2.54 (1.19-5.39) * | 1.00 | 1.45 (0.46-4.56) | 3.43 (1.32-8.89) * |
| Hyperglycemia (+) (N:2056) | | | | | | |
| N | 2001 | 39 | 16 | 2001 | 39 | 16 |
| Person-years of follow-up | 33345 | 516 | 186 | 33345 | 516 | 186 |
| Case | 220 | 8 | 4 | 99 | 6 | 3 |
| Mortality (/1000 person-years) | 6.60 | 15.50 | 21.51 | 2.97 | 11.63 | 16.13 |
| Age-adjusted hazard ratios | 1.00 | 1.22 (0.60-2.48) | 1.68 (0.62-4.53) | 1.00 | 2.32 (1.01-5.35) | 3.02 (0.95-9.55) |
| Multivariate-adjusted hazard ratios | 1.00 | 1.37 (0.67-2.82) | 1.26 (0.46-3.46) | 1.00 | 2.52 (1.09-5.86) * | 2.41 (0.74-7.79) |
| Hyperlipidemia (-) (N:5494) | | | | | | |
| N | 5410 | 63 | 21 | 5410 | 63 | 21 |
| Person-years of follow-up | 94128 | 1021 | 282 | 94128 | 1021 | 282 |
| Case | 310 | 6 | 4 | 143 | 6 | 3 |
| Mortality (/1000 person-years) | 3.29 | 5.88 | 14.19 | 1.52 | 5.88 | 10.64 |
| Age-adjusted hazard ratios | 1.00 | 0.92 (0.41-2.08) | 1.97 (0.73-5.28) | 1.00 | 2.07 (0.91-4.71) | 3.28 (1.04-10.31) * |
| Multivariate-adjusted hazard ratios | 1.00 | 1.06 (0.47-2.39) | 1.29 (0.47-3.56) | 1.00 | 2.19 (0.95-5.03) | 2.62 (0.81-8.48) |
| Hyperlipidemia (+) (N:2845) | | | | | | |
| N | 2785 | 45 | 15 | 2785 | 45 | 15 |
| Person-years of follow-up | 48792 | 681 | 196 | 48792 | 681 | 196 |
| Case | 207 | 9 | 8 | 97 | 3 | 5 |
| Mortality (/1000 person-years) | 4.24 | 13.21 | 40.81 | 1.99 | 4.40 | 25.51 |
| Age-adjusted hazard ratios | 1.00 | 2.50 (1.28-4.88) * | 3.19 (1.55-6.55) * | 1.00 | 1.85 (0.59-5.84) | 5.14 (2.05-12.89) * |
| Multivariate-adjusted hazard ratios | 1.00 | 2.33 (1.19-4.56) * | 2.35 (1.09-5.06) * | 1.00 | 1.67 (0.53-5.28) | 3.96 (1.51-10.39) * |

Values in parentheses indicate 95% confidence interval of hazard ratios. The mark, *, indicates statisitically significant increase compared to the reference .
Diagnosis for the presence of hypertension: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or current medication for hypertension.
Diagnosis for the presence of hyperglycemia: blood sugar ≥ 140 mg/dl and/or the presence of history of diabetes mellitus .
Diagnosis for the presence of hyperlipidemia: total cholesterol ≥ 200 mg/dl.
The age-adjusted hazard ratio: the grade of q wave abnormality, sex, and age at study entry were entered in the model.
The multivariate-adjusted hazard ratio: the grade of q wave abnormality, sex, age at study entry, systolic blood pressure, body mass index, serum total cholesterol, smoking habit, alcohol drinking, and the presence of hyperglycemia (glucose ≥ 140 mg/dl and/or the presence of history of diabetes mellitus) were entered in the model.

# 脳卒中家族歴・高血圧家族歴と脳卒中死亡の関連;
# NIPPON DATA80 19年間追跡における検討

研究協力者　門田 文　　滋賀医科大学社会医学講座公衆衛生学部門
研究協力者　寶澤 篤　　東北大学大学院社会医学講座公衆衛生学分野 助教
研究分担者　岡村 智教　国立循環器病センター予防検診部 部長
研究代表者　上島 弘嗣　滋賀医科大学社会医学講座公衆衛生学部門 教授

【背景および目的】家族歴は遺伝的素因を反映すると考えられるが遺伝子と異なり問診等で容易に入手できる。また高血圧は循環器疾患の重要な危険因子であるが、これも家族歴との関連が示唆されている。本邦は脳卒中発症率が欧米と比較して非常に多かったという歴史的背景を持つが、これまで家族歴と脳卒中の関連は1970年代のOkadaらの報告以降ほとんど検討されていない。本研究では脳卒中死亡リスクと家族歴の関連について検討した。

【方法】NIPPON DATA80コホートから循環器疾患既往を持つ者やデータ欠損等を除いた8037人を19年間追跡した。本研究では両親のいずれかに“病歴あり”と回答した者を“家族歴あり”と定義した。Cox 比例ハザードモデルを用いて脳卒中家族歴および高血圧家族歴それぞれについて“家族歴なし”を対照群として脳卒中死亡のハザード比(HR)ならびに95%信頼区間（95%CI）を算出した。年齢、血圧、総コレステロール、血糖値、喫煙習慣、飲酒習慣を調整因子とした。

【結果】19年の追跡期間中、総死亡1570人と脳卒中死亡261人(脳梗塞152人、脳出血58人、その他の脳卒中 51 人)が確認された。脳卒中家族歴の脳卒中死亡 HR は男性 0.73 (0.47-1.15),女性 1.38(0.89-2.14)であり、男女ともに脳卒中死亡との関連を認めなかった。一方、高血圧家族歴では、男性では脳卒中死亡 HR1.36 (0.96-1.93)、脳梗塞死亡 HR1.68(1.08-2.60)であり、脳梗塞では統計的に有意な関連を認めた。しかし、女性では関連を認めなかった。年齢で60歳未満の若年層と60歳以上の高齢層に分けて検討した。高血圧家族歴は、男性の若年層では脳卒中死亡との関連を認めなかったが、高齢層では脳卒中死亡 HR はあまり大きくはないものの 1.52(1.02-2.27)と統計的に有意であった。一方、女性では若年層の脳卒中死亡 HR は 3.06(1.37-6.86)と有意な関連を示したが、高齢層では関連は認めなかった。

【結論】脳卒中家族歴は脳卒中死亡と関連を認めなかった。その理由として対象者の両親が脳卒中を発症した時代背景、すなわち非常に高い塩分摂取量や重労働、低栄養など現在とは異なる環境要因が存在しており、遺伝的な素因の如何に関わらず多くの人が脳卒中に罹患した時代であったことや当時の診断技術等が影響していると考えられる。一方、高血圧家族歴は女性の若年層、及び男性の高齢層で脳卒中死亡との関連を認めた。高血圧の家

族歴を問診等で聴取した場合、現時点で高血圧がなくても他の脳卒中の危険因子に対する介入、すなわち、食事・運動を中心とした生活指導等が必要である。また将来の高血圧の発症にも注意する必要がある。

表1. 脳卒中家族歴、高血圧家族歴と脳卒中死亡ハザード比（95%信頼区間）年齢層別解析　30歳以上一般住民 男性3,586人女性4,451 人 (NIPPON DATA80, 1980-1999).

| | 男性 家族歴 | | | | 女性 家族歴 | | | |
|---|---|---|---|---|---|---|---|---|
| | 脳卒中 | | 高血圧 | | 脳卒中 | | 高血圧 | |
| | なし | あり | なし | あり | なし | あり | なし | あり |
| (a)60歳未満 | | | | | | | | |
| 観察数 | 2199 | 559 | 1883 | 875 | 2676 | 719 | 2348 | 1047 |
| 観察人年 | 40085 | 10144 | 34412 | 15817 | 49918 | 13300 | 43811 | 19407 |
| 全脳卒中 | | | | | | | | |
| 死亡数 | 26 | 8 | 22 | 12 | 20 | 5 | 11 | 14 |
| *HR(95%CI) | 1.00 | 1.19(0.53-2.69) | 1.00 | 1.10(0.54-2.27) | 1.00 | 0.74(0.27-2.00) | 1.00 | 3.18(1.42-7.11) |
| **HR(95%CI) | 1.00 | 1.30(0.57-2.96) | 1.00 | 1.03(0.50-2.14) | 1.00 | 0.72(0.26-1.95) | 1.00 | 3.06(1.37-6.86) |
| ***HR(95%CI) | 1.00 | 1.31(0.57-3.00) | 1.00 | 1.04(0.50-2.16) | 1.00 | 0.65(0.24-1.78) | 1.00 | 3.41(1.49-7.81) |
| (b) 60歳以上 | | | | | | | | |
| 観察数 | 654 | 174 | 559 | 269 | 852 | 204 | 749 | 307 |
| 観察人年 | 8720 | 2355 | 7514 | 3561 | 12881 | 2937 | 11233 | 4585 |
| 全脳卒中 | | | | | | | | |
| 死亡数 | 89 | 16 | 63 | 42 | 75 | 22 | 71 | 26 |
| *HR(95%CI) | 1.00 | 0.58(0.34-1.00) | 1.00 | 1.50(1.01-2.23) | 1.00 | 1.42(0.88-2.30) | 1.00 | 0.81(0.52-1.28) |
| **HR(95%CI) | 1.00 | 0.58(0.34-1.01) | 1.00 | 1.52(1.02-2.27) | 1.00 | 1.54(0.95-2.50) | 1.00 | 0.76(0.48-1.20) |
| ***HR(95%CI) | 1.00 | 0.58(0.34-1.00) | 1.00 | 1.50(1.00-2.24) | 1.00 | 1.57(0.97-2.57) | 1.00 | 0.77(0.49-1.23) |

HR: ハザード比 CI: 信頼区間
*HRはCox比例ハザードモデルで年齢を調整
**HRはCox比例ハザードモデルで年齢,血糖,総コレステロール,喫煙習慣,飲酒習慣を調整
***HRはCox比例ハザードモデルで年齢,収縮期血圧,血糖,総コレステロール,喫煙習慣,飲酒習慣を調整

【研究成果公表論文】

**Aya KADOTA, Tomonori OKAMURA, Atsushi HOZAWA, Takashi KADOWAKI, Yoshitaka MURAKAMI, Takehito HAYAKAWA, Yoshikuni KITA, Akira OKAYAMA, Yasuyuki NAKAMURA, Hirotsugu UESHIMA. Relationships between Family histories of stroke and of hypertension and Stroke Mortality: NIPPON DATA80, 1980-1999**

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# Relationships between Family Histories of Stroke and of Hypertension and Stroke Mortality: NIPPON DATA80, 1980-99

**Authors:**
Aya KADOTA[1,2], MD, Tomonori OKAMURA [3], MD, Atsushi HOZAWA [4], MD, Takashi KADOWAKI[1], MD, Yoshitaka MURAKAMI[1], PhD, Takehito HAYAKAWA[5], PhD, Yoshikuni KITA[1], PhD, Akira OKAYAMA[6], MD, Yasuyuki NAKAMURA[7], MD and Hirotsugu UESHIMA[1], MD for the NIPPON DATA Research Group[+]

[1]Department of Health Science, Shiga University of Medical Science,
Otsu, Japan
[2]Department of Internal Medicine, Shiga University of Medical Science,
Otsu, Japan
[3]Department of Preventive Cardiology, National Cardiovascular Center,
Suita, Japan
[4]Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine
Sendai, Japan
[5]Department of Hygiene and Preventive Medicine, Fukushima Medical University,
Fukushima, Japan
6The First Institute of Health Service, Japan Anti-Tuberculosis Association,
Tokyo, Japan
[7]Cardiovascular Epidemiology, Kyoto Women's University
[+]Members of the Research Group are listed in the reference 6.

**Short running title:** Family history and stroke mortality

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**Corresponding Author:**
Aya Kadota, MD
Department of Health Science, Shiga University of Medical Science
Seta Tsukinowa-cho, Otsu 520-2192, Japan
Tel: +81-77-548-2191
Fax: +81-77-543-9732
E-mail: ayakd@belle.shiga-med.ac.jp

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**Abstract**

A family history of stroke seems to be related with increased risk of stroke although the relationship is not always significant. Increased risk of stroke is strongly associated with hypertension, which might be also associated with family history. However, investigations into the relationship between family history of hypertension and stroke mortality are scarce. We investigated whether a family history of stroke and that of hypertension evaluated using a simple questionnaire could predict stroke mortality in Japanese.

We obtained parental histories of stroke and of hypertension from 8,037 randomly selected general Japanese without history of cardiovascular disease and followed them for 19 years. The multivariate adjusted hazard ratios (HRs) for total stroke mortality, intra-cerebral hemorrhage mortality and for cerebral infarction mortality according to family history were estimated using the Cox proportional hazards model.

The prevalences of family histories of stroke and of hypertension were 20.6% and 31.1%, respectively. A family history of stroke was not related to total stroke mortality, intra-cerebral hemorrhage mortality or to cerebral infarction mortality. Meanwhile, a family history of hypertension was positively related to total stroke mortality among women

aged less than 60 years and men aged 60 or more years (women: HR = 3.41, 95%CI: 1.49 – 7.81; men: HR = 1.50, 95%CI: 1.00 – 2.24) even after adjustment for systolic blood pressure.

In conclusion, a family history of stroke could not predict total stroke mortality. However, a family history of hypertension might predict an increased risk for total stroke.

**Key words:** family history, stroke, hypertension, stroke mortality, epidemiology

**Introduction**

One of the simplest ways to determine whether individuals have a potential genetic risk for diseases, even in developing countries, is to collect information about their family history. The 2002 American Heart Association guidelines for primary prevention of cardiovascular disease and stroke recommend regularly updating family histories for coronary heart disease (1).

Stroke is strongly affected by hypertension, which may also be associated with family history (2). Thus, knowledge of the family history of hypertension might also provide potential predictability for stroke. Nevertheless, the relationship between stroke mortality and a family history of stroke and of hypertension remains unclear except for the relationship between subarachnoid hemorrhage and a family history(3-4).

Although stroke mortality and incidence has remained still higher in Japan than in Western countries (5), very few prospective studies have examined the association between family history and stroke mortality in the general Japanese population. NIPPON DATA80 is a large cohort study of individuals selected randomly from all over Japan who were followed up for 19 years. We investigated whether a simple questionnaire about family histories of stroke and of hypertension could predict stroke mortality among the general Japanese population.

**Methods**

Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere(6).

A total of 10,546 residents (4640 men and 5906 women, aged ≥ 30 years) from 300 randomly selected districts participated in the survey and were followed up until November 1999. The overall population of residents over 30 years of age in all districts was 13,771, and the participation rate in the survey was 76.6%. Accordingly, these participants were considered to be representative of the Japanese population. Of the 10,546 participants, 2,509 were excluded due to incomplete residential access information at the first survey (n = 908), a history of coronary heart disease or stroke (n = 697), or missing information in baseline survey (n = 904). The present study analyzed data from the remaining 8,037 participants (3,586 men and 4,451 women). The prevalences of family histories of stroke and of hypertension did not differ between those who were followed up and those who were not.

Follow-up survey

The underlying causes of death in the National Vital Statistics which we obtained from the Ministry of Health, Labor and Welfare were coded according to the 9$^{th}$ International Classification of Diseases (ICD-9) until the end of 1994 and according to the 10$^{th}$ International Classification of Disease (ICD-10) from the start of 1995 until the end of 1999. The details of these classifications are described elsewhere (6). Codes 430-438 in ICD-9 and I60-69 in ICD-10 were defined as death from total stroke, which included death from cerebral infarction (codes 433, 434, 437.7a and 7b in ICD-9, I61 and I69.1 in ICD-10) and from intra-cerebral hemorrhage (codes 431-432 in ICD-9, I63 and I69.3 in ICD-10).

The Management and Coordination Agency of the Government of Japan provided permission to use the National Vital Statistics and the Institutional Review Board of Shiga University of Medical Science (No. 12 - 18, 2000) approved this study.

Baseline examination

Public health nurses obtained information about parental family histories of stroke and of hypertension (none, both parents, only paternal, only maternal). We defined a participant as "family history positive" if he or she reported that one parent had such a history. Public health nurses also obtained information about smoking, alcohol consumption, and medical history. Trained observers obtained baseline blood pressure values using a standard mercury sphygmomanometer placed on the right arm of seated participants. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Non-fasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (Osaka Medical Center for Health Science and Promotion) for blood measurements. Plasma glucose was measured using the cupric-neocuproine method and converted to the value of the glucose oxidase

method (7). Total cholesterol was also measured enzymatically as standardized by the Centers for Disease Control/National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipids Standardization Program (8).

We defined high blood pressure as systolic blood pressure of ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, the administration of antihypertensive agents, or any combination of these. We divided participants into five categories of smokers (never-smoked; ex-smoker; current smoker, <21 cigarettes/day, ≥21 cigarettes/day and ≥41 cigarettes/day) and four categories of drinking (never-drinker; ex-drinker; current drinker, occasionally and daily).

Statistical analysis

Continuous variables were compared using the analysis of variance and dichotomized variables were compared using the $\chi^2$-test to determine differences in the baseline characteristics according to family history categories. The multivariate adjusted hazard ratios (HRs) of stroke mortality were estimated by three Cox proportional hazards models with the following adjustments: Model 1, age; Model 2, age, total cholesterol, blood glucose, smoking, and drinking category; Model 3, systolic blood pressure was added to Model 2. All confidence intervals were estimated at the 95% level. All statistical tests were two-sided and significance was defined as $P < 0.05$. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) was used to perform all analyses.

**Results**

The prevalences of family histories of stroke and of hypertension were 20.6 and 31.1%, respectively. Table 1 shows the baseline characteristics of the study participants stratified by gender and age according to family histories. In both gender- and age-specific groups, participants with a family history of hypertension more often had a family history of stroke. We did not find any significant difference according to family history in mean values of age, BMI, blood pressure, total cholesterol, or blood glucose. In addition, the prevalences of hypertension, frequency of medication for hypertension, smoking, or alcohol consumption did not significantly differ.

Total person-years of follow-up were 140,340 and the mean follow-up period was 17.5 years. During this period, 1,570 participants died of all causes and 261 participants died of total stroke (152 of ischemic stroke, 58 of intra-cerebral hemorrhagic stroke and 51 of other conditions).

Table 2 shows gender specific analyses. The number of stroke deaths, multiple adjusted HRs and 95% CIs for stroke mortality according to family histories of stroke and of hypertension are listed. A family history of stroke was not related to stroke mortality in either gender. A family history of hypertension was positively and significantly related to cerebral infarction mortality in men (Table 2; total stroke, Model 2: HR = 1.38, 95%CI: 0.97 –1.96, cerebral infarction, Model 2: HR = 1.68, 95%CI: 1.08 – 2.60). On the other hand, a family history of hypertension did not predict stroke mortality in women.

Table 3 shows gender- and age-group-specific analyses. A family history of stroke was not related to stroke mortality in either gender or any age specific group. A family history of hypertension did not relate to total stroke mortality in younger men aged <60 years but significantly increased total stroke mortality in elderly men aged ≥60 years (Table 3: Men (b); Model 2: HR = 1.52, 95%CI: 1.02 - 2.27). Conversely, in women, a family history of hypertension significantly increased total stroke mortality in younger group aged <60 years (Table 3: Women (a); Model 2: HR = 3.06, 95%CI: 1.37 - 6.86). Among elderly women aged ≥60 years, we did not find any relationship between family history of hypertension and stroke mortality (Table 3: Women (b)).We calculated all HRs using the three models and found that adjustment for systolic blood pressure did not alter these findings.

**Discussion**

The present study found that a family history of stroke could not predict stroke mortality in the general Japanese population. However, a family history of hypertension significantly related to stroke mortality among elderly men aged 60 or more years and younger women aged less than 60 years.

In previous epidemiologic investigations including studies of twins and the Framingham Study, a family history of stroke seemed to increase the risk of stroke although some studies did not find a significant relationship (4, 9-16). Floßmann et al. systematically reviewed the genetic epidemiology of ischemic stroke. Their meta-analyses identified a positive family history of stroke as a moderate risk factor for ischemic stroke in both case-control (odds ratio (OR): 1.76; 95%CI, 1.7 - 1.9) and cohort (OR: 1.3; 95%CI, 1.2 - 1.5) studies (4). Although possible confounding factors were not adjusted for, a prospective Japanese study showed that a family history of stroke increased the risk of intra-cerebral hemorrhage but not of cerebral infarction (11). Based on these findings, the American Heart Association/American Stroke Association Stroke Council noted that both paternal and maternal histories of stroke are associated with increased risk of stroke through many mechanisms, including (1) genetic heritability of stroke risk factors, (2) inheritance of susceptibility to the effects of such risk factors, (3) familial sharing of cultural/environmental and lifestyle factors, and (4) interaction between genetic and environmental factors (3).

On the bases of this information, we initially postulated that participants with a family history of stroke might have higher blood pressure, other unfavorable risk factors and consequently a higher HR for stroke mortality than those

without such a family history. However, we did not identify any significant associations. One possible explanation for the absence of a relationship between family history of stroke and stroke mortality might be the very high historical stroke mortality rate in Japan. Although the genetic pool of Japanese has not changed, the age-adjusted stroke mortality rate has significantly decreased during the past half-century (17). This suggests that environmental factors in the past, such as especially higher salt intake which lead to increased blood pressure or malnutrition, strongly contributed to the stroke incidence, especially that of cerebral hemorrhage (18). Furthermore, since infectious disease was frequent cause of death during the lifetimes of respondents' parents, there were also some possibilities that a positive family history of stroke in the present study included the parents who were afflicted with stroke because they simply lived longer. Thus, a family history of stroke assessed using the reports to a simple questionnaire in the present study could not predict stroke mortality in Japan. Differentiation of family history of stroke and age of stroke onset among afflicted parents might be important to understand the influence of a family history of stroke on stroke mortality (16).

Hypertension is one of the main risk factors for stroke, which is also supposed to be affected by family history (2,19). Several genetic epidemiologic studies have revealed that gene polymorphisms are related to hypertension (19-21). Some studies have also found an aggregation of hypertension and stroke in family histories and medical histories, suggesting a close association between these diseases (22-23). We also found an aggregation of both diseases in family histories in the present study. However, studies on the relationship between a family history of hypertension and stroke mortality are still scarce and the results are not concordant. Flossmann et al. mentioned the difficulty of diagnosing family history of hypertension in the past in their review (4). Okada et al. reported the prevalence of family history of hypertension was 5.4%(224 / 4,186) in 1976 (11), which was much lower than that observed in the present study. Recall for parental hypertension may be difficult to confirm because of less frequent opportunity for measuring blood pressure or different criteria of hypertension when their parents were young and alive and of so-called "recall bias". Thus, further study should be warranted. In our present findings, we observed the relationship between family history of hypertension and stroke mortality was evident with a significant HR greater than 3.0 among younger women than elder women and men. This suggests that some genetic influences are involved in the pathogenesis of hypertension and stroke (14–15), although HR of elder men was around 1.5 with statistical significance. We primarily hypothesized that the relation between family history of hypertension and stroke mortality was stronger in younger than that in elderly because the effect of environmental cardiovascular risk factors might be evident in the elderly and numbers of risk factors would increase with age (24), which attenuated the effect of family history due to genetic background. This hypothesis is consistent with our findings for women. Since the awareness of hypertension was reported to be lower in men than in women (25), lower accuracy of family history of hypertension in men might have lead to the low HR in younger men.

In conclusion, a simple questionnaire designed to assess a family history of stroke could not be an index of potential genetic risk predicting stroke mortality in this study. More specific information with regard to parental history of stroke or more specific genetic exploration might be required to assess the genetic risk of stroke mortality. Whereas a family history of hypertension obtained from a simple questionnaire might have the potential to predict an increased risk of total stroke mortality. For individuals who reported family history of hypertension, other cardiovascular risk factors and the risk factors for future hypertension such as salt intake (26), should be managed to prevent stroke.

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Table 1. Means and prevalence of baseline characteristics of 3,586 men and 4,451 women aged 30 years and older (NIPPON DATA80, 1980).

| Baseline risk characteristics | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Family history | | | | Family history | | | |
| | Stroke | | Hypertension | | Stroke | | Hypertension | |
| | No | Yes | No | Yes | No | Yes | No | Yes |
| (a) Age less than 60 | | | | | | | | |
| Number of participants | 2199 | 559 | 1183 | 875 | 2676 | 719 | 2348 | 1047 |
| Family history of stroke(%) | 0.0 | 100.0 | 14.4 | 32.8* | 0.0 | 100.0 | 14.8 | 35.4* |
| Age | 44.47±8.43 | 44.47±8.44 | 44.34±8.46 | 44.73±8.38 | 44.54±8.62 | 44.49±8.48 | 44.63±8.65 | 44.30±8.45 |
| BMI (kg/m$^2$) | 22.81±2.80 | 22.62±2.77 | 22.80±2.78 | 22.72±2.81 | 22.86±3.27 | 22.82±3.34 | 22.82±3.25 | 22.91±3.38 |
| Systolic Blood Pressure (mmHg) | 134.52±18.70 | 134.63±18.39 | 134.06±18.79 | 135.59±18.26 | 129.24±19.15 | 129.18±19.11 | 129.35±19.07 | 128.97±19.29 |
| Diastolic Blood Pressure (mmHg) | 83.21±12.13 | 82.56±12.41 | 82.78±12.03 | 83.72±12.50 | 78.27±11.64 | 79.28±11.67 | 78.22±11.36 | 79.07±12.27 |
| Total Cholesterol (mg/dl) | 188.15±33.31 | 185.77±32.23 | 187.67±32.96 | 187.66±33.41 | 187.28±32.69 | 186.42±35.06 | 186.81±32.52 | 187.76±34.69 |
| Blood glucose (mg/dl) | 100.34±32.17 | 98.73±25.33 | 99.52±29.61 | 101.07±33.52 | 98.17±26.65 | 96.06±19.53 | 98.63±27.77 | 95.70±18.56 |
| High blood pressure (%) | 35.1 | 37.6 | 34.5 | 37.9 | 25.1 | 26.6 | 25.2 | 25.9 |
| Medication for hyertension (%) | 7.1 | 6.8 | 7.3 | 6.5 | 7.8 | 9.0 | 7.7 | 8.9 |
| Drinking | | | | | | | | |
| non-drinker (%) | 21.8 | 19.3 | 21.6 | 20.7 | 78.4 | 78.4 | 77.8 | 79.9 |
| occasional-drinker (%) | 29.1 | 27.4 | 29.3 | 27.8 | 19.0 | 19.2 | 19.3 | 18.4 |
| current-drinker (%) | 49.1 | 53.3 | 49.1 | 51.5 | 2.6 | 2.4 | 2.9 | 1.7 |
| Smoking | | | | | | | | |
| non-smoker (%) | 33.7 | 34.7 | 33.4 | 35.2 | 92.0 | 91.8 | 92.4 | 91.1 |
| current-smoker(≤20) (%) | 37.2 | 35.8 | 38.0 | 34.7 | 7.3 | 7.4 | 7.0 | 8.0 |
| current smoker(21≤) (%) | 29.1 | 29.5 | 28.6 | 30.1 | 0.7 | 0.8 | 0.6 | 0.9 |
| (b) Age 60 and more | | | | | | | | |
| Number of participants | 654 | 174 | 559 | 269 | 852 | 204 | 749 | 307 |
| Family history of stroke(%) | 0.0 | 100.0 | 15.0 | 33.5* | 0.0 | 100.0 | 15.1 | 29.6* |
| Age | 69.06±6.35 | 68.54±6.04 | 68.67±6.05 | 69.12±6.75 | 68.71±6.29 | 69.01±6.87 | 68.66±6.20 | 69.03±6.87 |
| BMI (kg/m$^2$) | 21.78±2.91 | 21.77±3.09 | 21.74±2.90 | 21.86±3.03 | 22.77±3.54 | 22.78±3.53 | 22.79±3.54 | 22.74±3.51 |
| Systolic Blood Pressure (mmHg) | 150.24±20.87 | 150.22±20.94 | 150.32±22.49 | 150.06±22.45 | 147.32±22.59 | 144.85±22.61 | 147.64±22.78 | 144.88±22.09 |
| Diastolic Blood Pressure (mmHg) | 85.12±12.67 | 84.89±11.64 | 84.81±12.33 | 85.61±12.72 | 82.65±12.32 | 81.53±11.86 | 82.58±12.33 | 82.06±12.03 |
| Total Cholesterol (mg/dl) | 182.57±31.72 | 185.70±32.46 | 184.39±31.98 | 180.81±31.60 | 201.52±34.43 | 195.63±30.05 | 200.90±33.00 | 199.12±35.36 |
| Blood glucose (mg/dl) | 111.50±40.45 | 106.04±28.31 | 110.28±40.45 | 110.50±33.36 | 110.04±35.33 | 110.88±31.05 | 109.86±33.53 | 111.03±36.91 |
| High blood pressure (%) | 67.4 | 72.4 | 67.8 | 69.9 | 63.6 | 61.8 | 64.9 | 59.3 |
| Medication for hyertension (%) | 26.9 | 31.0 | 26.7 | 30.1 | 29.1 | 30.4 | 29.9 | 28.0 |
| Drinking | | | | | | | | |
| non-drinker (%) | 35.9 | 32.8 | 36.3 | 33.1 | 84.6 | 82.8 | 84.6 | 83.4 |
| occasional-drinker (%) | 20.6 | 17.2 | 18.8 | 22.3 | 11.3 | 12.7 | 11.2 | 12.4 |
| current-drinker (%) | 43.4 | 50.0 | 44.9 | 44.6 | 4.1 | 4.5 | 4.2 | 4.2 |
| Smoking | | | | | | | | |
| non-smoker (%) | 43.3 | 48.3 | 44.5 | 43.9 | 88.7 | 91.2 | 89.2 | 89.3 |
| current-smoker(≤20) (%) | 45.3 | 40.2 | 44.7 | 43.1 | 10.3 | 8.3 | 9.9 | 10.1 |
| current smoker(21≤) (%) | 11.4 | 11.5 | 10.8 | 13.0 | 1.0 | 0.5 | 0.9 | 0.6 |

BMI: body mass index

High blood pressure was defined as SBP≧140 mmHg and /or DBP≧90 mmHg and /or medication.

*:$p < 0.05$

Table 2. Multiple adjusted hazard ratios and 95% confidence intervals according to the family history by gender in 3,586 men and 4,451 women aged 30 years and older (NIPPON DATA80, 1980-1999).

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Family history | | | | Family history | | | |
| | Stroke | | Hypertension | | Stroke | | Hypertension | |
| | No | Yes | No | Yes | No | Yes | No | Yes |
| Number of participants | 2853 | 733 | 2442 | 1144 | 3528 | 923 | 3097 | 1354 |
| Person-years | 48805 | 12550 | 41926 | 19378 | 62799 | 16237 | 55044 | 23992 |
| All stroke | | | | | | | | |
| number of death | 115 | 24 | 85 | 54 | 95 | 27 | 82 | 40 |
| *HR(95%CI) | 1.00 | 0.70(0.45-1.10) | 1.00 | 1.40(0.99-1.99) | 1.00 | 1.27(0.82-1.95) | 1.00 | 1.11(0.75-1.62) |
| **HR(95%CI) | 1.00 | 0.73(0.47-1.15) | 1.00 | 1.38(0.97-1.96) | 1.00 | 1.32(0.85-2.04) | 1.00 | 1.08(0.73-1.59) |
| ***HR(95%CI) | 1.00 | 0.73(0.47-1.15) | 1.00 | 1.36(0.96-1.93) | 1.00 | 1.38(0.89-2.14) | 1.00 | 1.13(0.77-1.66) |
| Intra-cerebral hemorrhage | | | | | | | | |
| number of death | 28 | 6 | 22 | 12 | 18 | 6 | 13 | 11 |
| *HR(95%CI) | 1.00 | 0.77(0.31-1.88) | 1.00 | 1.19(0.58-2.44) | 1.00 | 1.26(0.49-3.23) | 1.00 | 1.93(0.85-4.37) |
| **HR(95%CI) | 1.00 | 0.77(0.31-1.90) | 1.00 | 1.16(0.56-2.39) | 1.00 | 1.36(0.52-3.51) | 1.00 | 1.87(0.82-4.26) |
| ***HR(95%CI) | 1.00 | 0.78(0.32-1.94) | 1.00 | 1.13(0.55-2.32) | 1.00 | 1.47(0.57-3.82) | 1.00 | 1.82(0.80-4.18) |
| Cerebral infarction | | | | | | | | |
| number of death | 72 | 14 | 49 | 37 | 52 | 14 | 49 | 17 |
| *HR(95%CI) | 1.00 | 0.61(0.34-1.10) | 1.00 | 1.69(1.10-2.61) | 1.00 | 1.35(0.74-2.45) | 1.00 | 0.76(0.44-1.33) |
| **HR(95%CI) | 1.00 | 0.64(0.35-1.15) | 1.00 | 1.68(1.08-2.60) | 1.00 | 1.41(0.78-2.57) | 1.00 | 0.74(0.42-1.29) |
| ***HR(95%CI) | 1.00 | 0.63(0.35-1.14) | 1.00 | 1.65(1.07-2.56) | 1.00 | 1.48(0.81-2.69) | 1.00 | 0.77(0.44-1.36) |

HR: hazard ratio, CI: confidence interval,

*Hazard ratios were estimated by Cox proportional hazard model adjusted for age.

**Hazard ratios were estimated by Cox proportional hazard model adjusted for age, blood glucose, total cholesterol, smoking habits and drinking habits.

***Hazard ratios were estimated by Cox proportional hazard model adjusted for age, systoric blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits.

Table 3. Multiple adjusted hazard ratios and 95% confidence intervals according to the family history by gender and age specific group in 3,586 men and 4,451 women aged 30 years and older (NIPPON DATA80, 1980-1999).

| | Men | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|
| | Family history | | | | Family history | | | |
| | Stroke | | Hypertension | | Stroke | | Hypertension | |
| | No | Yes | No | Yes | No | Yes | No | Yes |
| (a) Age less than 60 | | | | | | | | |
| Number of participants | 2199 | 559 | 1883 | 875 | 2676 | 719 | 2348 | 1047 |
| Person-years | 40085 | 10144 | 34412 | 15817 | 49918 | 13300 | 43811 | 19407 |
| All stroke | | | | | | | | |
| number of death | 26 | 8 | 22 | 12 | 20 | 5 | 11 | 14 |
| *HR(95%CI) | 1.00 | 1.19(0.53-2.69) | 1.00 | 1.10(0.54-2.27) | 1.00 | 0.74(0.27-2.00) | 1.00 | 3.18(1.42-7.11) |
| **HR(95%CI) | 1.00 | 1.30(0.57-2.96) | 1.00 | 1.03(0.50-2.14) | 1.00 | 0.72(0.26-1.95) | 1.00 | 3.06(1.37-6.86) |
| ***HR(95%CI) | 1.00 | 1.31(0.57-3.00) | 1.00 | 1.04(0.50-2.16) | 1.00 | 0.65(0.24-1.78) | 1.00 | 3.41(1.49-7.81) |
| (b) Age 60 and more | | | | | | | | |
| Number of participants | 654 | 174 | 559 | 269 | 852 | 204 | 749 | 307 |
| Person-years | 8720 | 2355 | 7514 | 3561 | 12881 | 2937 | 11233 | 4585 |
| All stroke | | | | | | | | |
| number of death | 89 | 16 | 63 | 42 | 75 | 22 | 71 | 26 |
| *HR(95%CI) | 1.00 | 0.58(0.34-1.00) | 1.00 | 1.50(1.01-2.23) | 1.00 | 1.42(0.88-2.30) | 1.00 | 0.81(0.52-1.28) |
| **HR(95%CI) | 1.00 | 0.58(0.34-1.01) | 1.00 | 1.52(1.02-2.27) | 1.00 | 1.54(0.95-2.50) | 1.00 | 0.76(0.48-1.20) |
| ***HR(95%CI) | 1.00 | 0.58(0.34-1.00) | 1.00 | 1.50(1.00-2.24) | 1.00 | 1.57(0.97-2.57) | 1.00 | 0.77(0.49-1.23) |

HR: hazard ratio, CI: confidence interval,

*Hazard ratios were estimated by Cox proportional hazard model adjusted for age.

**Hazard ratios were estimated by Cox proportional hazard model adjusted for age, blood glucose, total cholesterol, smoking habits and drinking habits.

***Hazard ratios were estimated by Cox proportional hazard model adjusted for age, systoric blood pressure, blood glucose, total cholesterol, smoking habits and drinking habits.

# 喫煙による循環器疾患の過剰死亡はメタボリックシンドロームより大きい
## -NIPPON DATA90-


研究協力者　高嶋 直敬　滋賀医科大学社会医学講座公衆衛生学部門 特任助教
研究分担者　三浦 克之　滋賀医科大学社会医学講座公衆衛生学部門 准教授
研究協力者　寶澤 篤　東北大学大学院社会医学講座公衆衛生学分野 助教
研究協力者　門田 文　滋賀医科大学社会医学講座公衆衛生学部門
研究分担者　岡村 智教　国立循環器病センター予防検診部 部長
研究分担者　中村 保幸　京都女子大学家政学部生活福祉学科 教授
研究分担者　早川 岳人　福島県立医科大学衛生学・予防医学講座 講師
研究協力者　奥田 奈賀子　滋賀医科大学社会医学講座公衆衛生学部門 特任助教
研究協力者　藤吉 朗　滋賀医科大学社会医学講座公衆衛生学部門
研究協力者　門脇 崇　滋賀医科大学社会医学講座公衆衛生学部門 助教
研究協力者　村上 義孝　滋賀医科大学社会医学講座医療統計学部門 准教授
研究分担者　喜多 義邦　滋賀医科大学社会医学講座公衆衛生学部門 講師
研究分担者　岡山 明　財団法人結核予防会第一健康相談所 所長
研究代表者　上島 弘嗣　滋賀医科大学社会医学講座公衆衛生学部門 教授


肥満や喫煙は循環器疾患の重要な危険因子である。近年、日本やアジア諸国において肥満やメタボリックシンドロームの割合が増加しており、日本においては2008年よりメタボリックシンドロームに着目した特定健診・特定保健指導が開始された。しかし、これらの地域の喫煙率は男性で約40%と依然として高い割合を保っている。またアジア=太平洋地域では喫煙による循環器の過剰死亡は30%を超えることが報告されている。これらの研究から日本やアジア諸国においてもメタボリックシンドロームと喫煙による循環器の過剰死亡に占める割合が高いことが考えられるが、これまでに検討されていない。

本研究では喫煙とメタボリックシンドロームとの組み合わせでそれぞれの過剰死亡についてNIPPON DATA90をもちいて検討した。

### 方法

1990年に日本全国からランダムに抽出された300地区の保健所おいて調査に協力した8383名を15年間追跡した NIPPON DATA90を用いた。本研究では、30歳から70歳未満の男女7329名を対象とし、うち379名は循環器疾患の既往(249名)、ベースライン調査時のデータの欠落(130名)を除外した6650名(男性2752名、女性3898名)で解析を行った。

15年間追跡した NIPPON DATA90を用いてハザード比(HR)をCOX比例ハザードモデルを用いて解析を行った。さらに循環器疾患の過剰死亡、人口寄与危険割合(PAF)について計算した。メタボリックシンドロームは本邦の診断基準に準じ、血圧高値は血圧≥130/85mmHgまたは降圧薬治療中、高血糖は血中グルコース濃度≥110mg/dl または糖尿病治療中、脂質異常は中性脂肪≥150mg/dl、またはHDLコレステロール<40mg/dlまたは

脂質異常症にて治療中を、またBMI25以上を肥満ありとした。循環器死亡のハザード比は年齢と飲酒歴を調整してCOX比例ハザードモデルを用いて解析を行った。非喫煙、非肥満あるいは非メタボリックシンドロームのものをリファレンスとした。人口寄与危険割合（PAF）は*pd*×(HR-1)/HR で計算した（*pd*はそれぞれのカテゴリでの死亡した人の割合)。

結果

1990年調査時点の基本特性を表1に示した。平均年齢は男性49.9±11.2歳、女性49.0±11.3歳であった。喫煙率は男性58.0%、女性9.6%、血圧高値のものは男性66.9% 、女性54.4% であったが、肥満者は男性25.1%、女性23.4% であった。

追跡期間中に男性87名、女性61名の循環器死亡を確認した。図2では肥満と喫煙におけるHRとPAFを示した。肥満の有無にかかわらず、喫煙者でCVD死亡と正の関連を認めた。非肥満の非喫煙者と比較して、非肥満の喫煙者のHRは男性が3.13, (95% confidence interval [CI]: 1.33-7.36)、女性HR=4.32, (1.99-9.37)であった。非肥満喫煙者のCVD過剰死亡は男性32.0、女性6.9であった。非肥満の喫煙者と肥満の喫煙者の男性のPAFは36.8%と9.1%であった。女性では非肥満の喫煙者、肥満の非喫煙者、肥満の喫煙者のPAFはそれぞれ11.3%、0.5%、5.2%であった。

図3にはメタボリックシンドロームと喫煙で層別化したCVD死亡についてのHRとPAFについて示した。メタボリックシンドロームのない非喫煙者を1とした時に、メタボリックシンドロームのない喫煙者のHRは男性が3.47 (1.48- 8.12)、女性が3.63 (1.75-7.50)、メタボリックシンドロームのある喫煙者のHRは男性が3.19 (1.13-9.03)、女性が4.94 (1.52-16.09)であった。メタボリックシンドロームのない喫煙者では過剰死亡（PAF）は男性35.6名(40.9%)、女性7.2名(11.9%)で喫煙の有無にかかわらずメタボリックシンドロームのある男性7.4名(8.5%)、女性3.0名(5.0%)と比較して大きかった。

結論

われわれの結果ではメタボリックシンドロームのない喫煙者でもっとも大きな過剰死亡を認めた。この結果からメタボリックシンドロームの有無にかかわらず喫煙者に対する対策が循環器疾患予防に重要であると考えられる。この結果は喫煙率が高く、肥満者が比較的少ないアジア諸国にも適応できると考えらえる。

この他の多くの研究によってメタボリックシンドロームと喫煙は循環器疾患の重要な危険因子の一つであると考えられているが、日本人の循環器死亡においてどの程度の割合で寄与しているかについては検討されていない。この報告は日本人を代表する集団での15年追跡のデータを用いて初めて解析したものである。

喫煙率は欧米に比べて日本を含むアジア諸国では高く、さらに女性においては増加している。一方でメタボリックシンドロームの割合も増加してきている。しかしこのような状況