HbA$_{1c}$ and the Risks for All-Cause and Cardiovascular Mortality in the General Japanese Population

NIPPON DATA90

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RESEARCH DESIGN AND METHODS—The risk for cardiovascular death was evaluated in a large cohort of participants selected randomly from the overall Japanese population. A total of 7,120 participants (2,962 men and 4,158 women; mean age 52.3 years) free of previous CVD were followed for 15 years. Adjusted hazard ratios (HRs) and 95% CIs among categories of HbA$_{1c}$ were calculated using a Cox proportional hazards model.

RESULTS—During the study, there were 1,104 deaths, including 304 from CVD, 61 from coronary heart disease, and 127 from stroke (78 from cerebral infarction, 25 from cerebral hemorrhage, and 24 from unclassified stroke). Relations to HbA$_{1c}$ with all-cause mortality and CVD death were graded and continuous, and multivariate-adjusted HRs for CVD death in participants with HbA$_{1c}$ of 5.0%, 5.0–5.4%, 5.5–5.9%, 6.0–6.4%, and ≥6.5% for participants without treatment for diabetes and HRs for participants with diabetes were calculated using a Cox proportional hazards model.

CONCLUSIONS—High HbA$_{1c}$ levels were associated with increased risk for all-cause mortality and death from CVD, coronary heart disease, and cerebral infarction in general East Asian populations, as in Western populations.

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heart disease, cerebral infarction, and cerebral hemorrhage) in a 15-year cohort study of representative Japanese men and women randomly selected from the overall Japanese population.

RESEARCH DESIGN AND METHODS—NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease And its Trends in the Aged) is a cohort study of participants in the National Survey on Circulatory Disorders of Japan, which has been conducted by the Ministry of Health, Labor and Welfare of Japan. NIPPON DATA includes two cohort studies in which the baseline data were surveyed in 1980 (NIPPON DATA80) and in 1990 (NIPPON DATA90); the details of the studies have previously been described (16–21). Here, we investigated the data from NIPPON DATA90 because HbA1c was not measured in the NIPPON DATA80 baseline survey.

A total of 8,383 residents (3,503 men and 4,880 women, aged ≥30 years) from 300 randomly selected districts from all over Japan participated in the baseline survey and were followed until November 2005. The participation rate in this survey was 76.5%. Of the 8,383 participants, 1,263 were excluded because of a history of coronary heart disease or stroke (n = 358), missing information in the baseline survey (n = 649), or incomplete residential address information (n = 256). The remaining 7,120 participants (2,962 men and 4,158 women) were analyzed in the current study. The institutional review board of Shiga University of Medical Science (no. 12-18, 2000) approved this study.

Baseline examination
BMI was calculated as weight in kilograms divided by the square of height in meters. Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants. Nonfasting blood samples were obtained at the baseline survey. Serum was separated by centrifugation soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (SRL, Tokyo, Japan) for blood measurements. HbA1c was measured using the high-performance liquid chromatography method. The range of coefficient of variance of HbA1c measurement in this laboratory was 1.19–1.79% intra-assay and 0.24–0.45% interassay in the 1990s. HbA1c (JDS) values were converted to HbA1c (NGSP) values using the conversion formula provided by JDS: HbA1c, NGSP value (%) = 1.02 × JDS value (%) + 0.25 (14). All present analyses adopted the HbA1c values of the NGSP method. Serum total cholesterol (milligrams per deciliter) was measured using an enzymatic method, and HDL cholesterol was measured after heparin-calcium precipitation (22). Public health nurses collected the information about smoking, alcohol consumption, habitual exercise, and medical history. Treatment for diabetes was self-reported, which included diet, exercise, and medication with regular visits to hospitals.

End points
We reported previously that participants who had died in each area were confirmed by computer matching with data from the National Vital Statistics database, using area, sex, date of birth, and death as key codes (16,23). The underlying causes of death in the National Vital Statistics were coded according to the ICD-9 until 1994 and according to the ICD-10 from 1995. Details of these classifications have previously been described (16,17,20,23). Deaths coded were defined as follows: CVD, from 393 to 459 (ICD-9) and from 100 to 199 (ICD-10); coronary heart disease, from 410 to 414 (ICD-9) and from 120 to 125 (ICD-10); stroke, from 430 to 438 (ICD-9) and from 160 to 169 (ICD-10); cerebral infarction, 433, 434, 437.8a, and 437.8b (ICD-9) and 163 and 169–3 (ICD-10); cerebral hemorrhage, from 431 to 432 (ICD-9) and 161 and 169.1 (ICD-10).

Statistical analysis
Participants were divided into six groups; five groups of participants without treatment for diabetes according to HbA1c level, <5.0% (31 mmol/mol), 5.0–5.4% (31–36 mmol/mol), 5.5–5.9% (37–41 mmol/mol), 6.0–6.4% (42–47 mmol/mol), and ≥6.5% (48 mmol/mol), and one group for participants with treatment for diabetes. One-way ANOVA or the χ² test was used to compare characteristics of participants at baseline according to HbA1c categories. We calculated crude mortality and hazard ratios (HRs) for death due to all causes, CVD, coronary heart disease, stroke, cerebral infarction, and cerebral hemorrhage according to the six categories. The Cox proportional hazards model was used to calculate adjusted HRs. Adjustment for possible confounders was performed sequentially: for age and sex (age- and sex-adjusted model), then plus BMI, smoking habit (non-, ex-, or current smoker), drinking habit (non-, ex-, or daily drinker), habitual exercise (yes or no), systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia (multivariate-adjusted model). HRs for death associated with a 1% increment in HbA1c were calculated for participants without treatment for diabetes. HRs were also calculated separately for each sex, and the interaction between sex and HbA1c on the mortality from each cause of death was calculated. As HbA1c was affected by anemia (24), we evaluated the HRs for participants without anemia (n = 5,978) for sensitivity analyses. Anemia was defined as hemoglobin concentration <13.5 g/dL for men and <12.0 g/dL for women. The statistical analysis package SPSS 17.0 for Windows (SPSS, Chicago, IL) was used for all statistical analyses. All probability values were two tailed, and the significance level was set at P < 0.05.

RESULTS—The baseline characteristics of study participants are shown in Table 1. The mean age at baseline was 52.3 years, and the mean BMI was 22.9 kg/m². The mean HbA1c level was 5.3% (34 mmol/mol). Participants with higher HbA1c levels were older and had higher values for BMI, systolic and diastolic blood pressure, and serum total cholesterol; lower HDL cholesterol levels; and higher smoking rates.

There were 99,605 person-years of follow-up for the 7,120 participants. Among all of the participants, there were 1,104 deaths, including 304 deaths from CVD, 61 from coronary heart disease, and 127 from stroke (78 from cerebral infarction, 25 from cerebral hemorrhage, and 24 from unclassified stroke). Mortality and adjusted HRs according to HbA1c categories are shown in Table 2. The multivariate-adjusted HR for CVD death associated with a 1% increment in HbA1c was 1.32. Relations to HbA1c with CVD death were graded and continuous, and the multivariate-adjusted HR for CVD death in participants with HbA1c 6.0–6.4% (42–47 mmol/mol) was 2.18 (95% CI 1.22–3.87), and that in participants with HbA1c ≥6.5% (48 mmol/mol) was 2.75 (1.43–5.28); both HRs were significantly higher than that in participants with HbA1c <5.0% (31 mmol/mol). Similarly, HR for CVD death in participants with treatment for diabetes was 2.04 (1.19–3.50) and was significantly higher than that in participants with HbA1c <5.0% (31 mmol/mol). Similar associations were
| Characteristics | Any HbA1c (<3%) | >3% | >5.4% | >6.0% | >6.4% | >7.0% | >7.4% | >7.8% | >8.3% | >8.8% |
|-----------------|-----------------|-----|-------|-------|-------|-------|-------|-------|-------|-------|
| Patients with | (23-79 mmol/mol) | (70-126 mmol/mol) | (115-179 mmol/mol) | (150-199 mmol/mol) | (190-239 mmol/mol) | (240-279 mmol/mol) | (280-329 mmol/mol) | (330-379 mmol/mol) | (380-429 mmol/mol) | (430-479 mmol/mol) |
| Age (years) | 72.3 | 1.6 | 2.3 | 1.6 | 1.3 | 1.2 | 1.1 | 1.0 | 1.0 | 0.9 |
| BMI (kg/m²) | 28.4 | 1.0 | 1.2 | 1.1 | 1.0 | 0.9 | 0.9 | 0.8 | 0.8 | 0.8 |
| HbA1c (mmol/mol) | 47 | 1.8 | 2.3 | 1.7 | 1.9 | 1.7 | 1.6 | 1.6 | 1.5 | 1.5 |
| Total cholesterol (mg/dL) | 193 | 3.6 | 4.0 | 3.6 | 3.8 | 3.6 | 3.3 | 3.2 | 3.2 | 3.0 |
| HDL cholesterol (mg/dL) | 47 | 2.0 | 2.3 | 2.0 | 2.2 | 2.0 | 1.9 | 1.8 | 1.8 | 1.7 |
| Systolic blood pressure (mmHg) | 134 | 3.2 | 3.5 | 3.1 | 3.3 | 3.1 | 2.8 | 2.7 | 2.7 | 2.5 |

CONCLUSIONS—In the present prospective, community-based study in Japan, there was a significant positive association between HbA1c and the risk for all-cause mortality and death from death from coronary heart disease, and death from coronary artery disease. The association was significant for all-cause mortality and death from coronary artery disease and death from coronary artery disease and death from myocardial infarction. The association was not significant for death from death from cerebral hemorrhage. The association was significant for death from death from cerebral hemorrhage. The association was significant for death from death from cerebral hemorrhage. The association was significant for death from death from cerebral hemorrhage. The association was significant for death from death from cerebral hemorrhage.
Table 2—Risk of death according to the baseline HbA1c levels in 7,120 participants: NIPPON DATA90, 1990–2005

| HbA1c in participants without treatment for diabetes | Participants with treatment for diabetes | HbA1c 1% increment † |
|-----------------------------------------------|----------------------------------------|-----------------------|
| <5.0% (<31 mmol/mol) | 30,864 | 2,372 | 2,327 |
| 5.0–5.4% (31–36 mmol/mol) | 49,192 | 31 | 71 |
| 5.5–5.9% (37–41 mmol/mol) | 13,123 | 63 | 66 |
| 6.0–6.4% (42–47 mmol/mol) | 2,372 | 31 | 30 |
| ≥6.5% (≥48 mmol/mol) | 1,727 | 71 | 70 |

Person-years of follow-up

| Cases | Mortality (per 1,000 person-years) | Multivariate-adjusted HR (95% CI)* |
|-------|------------------------------------|-----------------------------------|
| All-cause death | | |
| | 199 | 6.4 | 1.00 (ref.) |
| | 529 | 10.8 | 1.04 (0.89–1.23) |
| | 211 | 16.1 | 1.01 (0.83–1.23) |
| | 63 | 26.6 | 1.75 (1.32–2.33) |
| | 31 | 17.9 | 1.61 (1.11–2.36) |
| | 71 | 17.9 | 1.66 (1.26–2.19) |
| Death from CVD | | |
| | 44 | 1.4 | 1.00 (ref.) |
| | 147 | 3.0 | 1.28 (0.91–1.79) |
| | 64 | 4.9 | 1.32 (0.89–1.94) |
| | 17 | 7.2 | 2.11 (1.21–3.70) |
| | 12 | 6.9 | 2.83 (1.50–5.37) |
| | 20 | 8.6 | 2.02 (1.19–3.43) |
| Death from coronary heart disease | | |
| | 9 | 0.3 | 1.00 (ref.) |
| | 27 | 1.2 | 1.20 (0.57–2.56) |
| | 14 | 4.9 | 1.55 (0.67–3.59) |
| | 2 | 0.8 | 1.23 (0.27–5.69) |
| | 2 | 1.7 | 3.45 (0.93–12.7) |
| | 3 | 6.9 | 3.10 (1.10–8.77) |
| | 6 | 8.6 | 1.38 (1.01–1.87) |
| Death from stroke | | |
| | 20 | 0.6 | 1.00 (ref.) |
| | 60 | 1.2 | 1.20 (0.57–2.56) |
| | 29 | 2.2 | 1.55 (0.67–3.59) |
| | 9 | 0.8 | 1.23 (0.27–5.69) |
| | 3 | 1.7 | 3.45 (0.93–12.7) |
| | 6 | 8.6 | 3.10 (1.10–8.77) |
| | 6 | 8.6 | 1.38 (1.01–1.87) |
| Death from cerebral infarction | | |
| | 8 | 0.3 | 1.00 (ref.) |
| | 42 | 0.9 | 1.14 (0.69–1.89) |
| | 15 | 1.1 | 1.30 (0.73–2.30) |
| | 5 | 2.2 | 2.48 (1.13–5.45) |
| | 2 | 0.8 | 1.58 (0.47–5.31) |
| | 6 | 1.7 | 3.10 (1.03–8.77) |
| | 6 | 8.6 | 1.38 (1.01–1.87) |
| Death from cerebral hemorrhage | | |
| | 8 | 0.3 | 1.00 (ref.) |
| | 8 | 0.2 | 1.19 (0.71–1.99) |
| | 4 | 1.1 | 1.38 (0.76–2.48) |
| | 4 | 2.2 | 2.74 (1.21–6.18) |
| | 1 | 0.8 | 1.57 (0.46–5.38) |
| | 6 | 1.7 | 4.10 (0.55–3.55) |
| | 6 | 8.6 | 1.32 (1.12–1.56) |

*Adjusted for age, sex, BMI, smoking status, alcohol consumption, habitual exercise, systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia. †Participants with treatment for diabetes were excluded from the analyses.
was shown owing to the small number of cases. Our results demonstrate that HbA1c was significantly associated with not only all-cause mortality and death from CVD but also death from coronary heart disease in a Japanese population. The Atherosclerosis Risk in Communities Study showed that multivariate-adjusted HRs in participants with HbA1c 6.0–6.4% and ≥6.5% were 1.88 (95% CI 1.55–2.28) and 2.46 (1.84–3.28) for the incidence of coronary heart disease and 2.19 (1.58–3.05) and 2.96 (1.87–4.67) for ischemic stroke, respectively, compared with participants with HbA1c 5.0–5.5% (10). The European Prospective Investigation into Cancer (EPIC)-Norfolk study also evaluated the HbA1c categories and CVD death, and relative risk of the participants with HbA1c 5.5–6.9% was ~2.5 compared with the participants with HbA1c <5.0% (3). Thus, the relative strength of the association of HbA1c with CVD risk in Japanese people was similar to that in Western individuals.

Previous studies in Western countries indicated increased cardiovascular risk with an increase in HbA1c within the non-diabetic range (3–8,10,29). In the current study, participants with HbA1c 6.0–6.4% (42–47 mmol/mol) had a significantly increased risk of death from CVD and cerebral infarction. HbA1c values were more closely related to postprandial hyperglycemia than to fasting glucose levels (30). High-normal HbA1c levels, even within the nondiabetic range, may reflect the presence of impaired glucose tolerance and postprandial hyperglycemia, which are important risk factors for CVD (31). Individuals with an HbA1c level of 6.0–6.4% (42–47 mmol/mol) are at high risk for progression to diabetes (1) as well as high risk for CVD. Future public health campaigns targeting CVD and type 2 diabetes should focus on lifestyle and other risk factors in these high-risk individuals.

Significant linear associations between HbA1c and all-cause death and death from CVD were observed in our study. Recently, a J-shape relationship between HbA1c and all-cause mortality was reported in a study of the New Zealand general population (8). Participants with

### Table 3—Multivariate-adjusted HR* of death according to the baseline HbA1c levels in men, women, and participants without anemia: sensitivity analyses, NIPPON DATA90, 1990–2005

| HbA1c in participants without treatment for diabetes | Participants with treatment for diabetes |
|---------------------------------------------------|----------------------------------------|
| <5.0% (<31 mmol/mol)                              |                                       |
| 5.0–5.4% (31–36 mmol/mol)                         |                                       |
| 5.5–5.9% (37–41 mmol/mol)                         |                                       |
| 6.0–6.4% (42–47 mmol/mol)                         |                                       |
| ≥6.5% (≥48 mmol/mol)                              |                                       |

| All-cause death                                   |                                         |
|---------------------------------------------------|----------------------------------------|
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |
| Death from CVD                                    |                                         |
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |
| Death from coronary heart disease                 |                                         |
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |
| Death from stroke                                 |                                         |
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |
| Death from cerebral infarction                    |                                         |
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |
| Death from cerebral hemorrhage                    |                                         |
| Men (n = 2,962)                                   | 1.00 (ref.)                             |
| Women (n = 4,158)                                 | 1.00 (ref.)                             |
| Participants without anemia (n = 5,978)          | 1.00 (ref.)                             |

*Adjusted for age, sex, BMI, smoking status, alcohol consumption, habitual exercise, systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia.
HbA1c <4.0% (20 mmol/mol) had the highest mortality rates of those without diabetes, and the HR was 2.90 compared with participants with an HbA1c of 4.0–4.9% (20–30 mmol/mol). As discussed by the authors, it was difficult to determine whether the increased risk of mortality for participants with very low HbA1c levels was causal or merely a result of reserve causation due to preexisting disease. In our study, the number of participants with HbA1c <4.0% (20 mmol/mol) was too small (n = 15) to evaluate the risk of death.

The association between the incidence of hemorrhagic stroke and diabetes is controversial. Studies have indicated an increased risk for hemorrhagic stroke in individuals with diabetes diagnosed by fasting glucose levels (32); a decreased risk in individuals with overt diabetes (33); or no association in individuals with overt diabetes (34) or with diabetes defined by fasting (35), 1-h (36), or 2-h post-glucose load measurements (35). Similar to our results, those of one previous study showed no association between hemorrhagic stroke and HbA1c level (12). The etiology and pathophysiology of ischemic and hemorrhagic stroke are different (37), which may also indicate different risk factors for the two stroke subtypes.

The strength of the current study was that these data were from a large, nationally representative cohort, and thus our findings can be generalized to the whole Japanese population. Another strength lies in the large sample size and long-term follow-up period compared with those in other Asian studies. Therefore, we could evaluate the associations separately for subtypes of CVD. Third, most studies in Asian countries were from Japan and used JDS values for HbA1c, whereas our analyses used NGSP values for HbA1c, allowing our data to be compared with those from Western countries. The main limitation of this study was that because fasting glucose was not measured in all participants, analyses on fasting glucose could not performed. It is difficult to obtain fasting blood samples at a mass health check-up. However, fasting is not necessary for assessment of HbA1c, and our data suggested that HbA1c would facilitate assessment of CVD risk associated with glucose metabolism at mass health check-ups, even if a fasting blood sample is not obtained. Another limitation was that deaths from stroke, especially hemorrhagic stroke, were too few to detect any significant relationship. Similarly, the number of participants with very low HbA1c levels was too few to allow evaluation of the mortality risk in these individuals. Another limitation was that we did not have data for some CVD risk factors associated with glucose metabolism, such as waist circumference and fasting triglycerides levels. A further limitation was that we used a single measurement of HbA1c at baseline, which might have underestimated the relationship owing to regression dilution bias (38), and changes in HbA1c during the 15-year follow-up period were not taken into account.

In conclusion, HbA1c was significantly and positively associated with an increased risk for all-cause mortality and mortality from CVD and coronary heart disease in this long-term cohort from a representative Japanese population. A higher risk of CVD was observed even in participants with HbA1c levels of 6.0–6.4% (42–47 mmol/mol), which are below the threshold for diabetes. HbA1c is a useful marker of glucose metabolism for mass screening because fasting is not required for its assessment. Our results showed that HbA1c was associated with CVD death in general East Asian populations, as in Western populations. Further study is needed to establish whether the measurement of HbA1c is useful for cardiovascular risk assessment in general East Asian populations.

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M.S. performed the analysis, wrote the manuscript, and approved the final version of the manuscript. S.S. collected data, performed the analysis, wrote the manuscript, and approved the final version of the manuscript. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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