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

NIPPON DATA90

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OBJECTIVE—Associations between HbA_{1c} and cardiovascular diseases (CVD) have been reported mainly in Western countries. It is not clear whether HbA_{1c} measurements are useful for assessing CVD mortality risk in East Asian populations.

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} (<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.

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} 6.0–6.4% and ≥6.5% were 2.18 (95% CI 1.22–3.87) and 2.75 (1.43–5.28), respectively, compared with participants with HbA_{1c} <5.0%. Similar associations were observed between HbA_{1c} and death from coronary heart disease and death from cerebral infarction.

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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Since the association between HbA_{1c} and microangiopathy was established in patients with diabetes, HbA_{1c} has been used for not only the determination of glucose control among patients with diabetes but also the diagnosis of diabetes (1). Measurement of HbA_{1c} is also recommended for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (2) because the association between HbA_{1c} and the risk for cardiovascular disease (CVD) in general populations has been reported, mainly from Western countries (3–10).

There have been only a few studies regarding the associations between HbA_{1c} and CVD in Asian populations (11–13). Furthermore, these studies were from Japan, and HbA_{1c} measurements were expressed mainly using Japan Diabetes Society (JDS) values rather than National Glycohemoglobin Standardization Program (NGSP) values; thus, we cannot compare these results with those from Western countries. Recently, the JDS provided an equation for the conversion from HbA_{1c} (JDS) to HbA_{1c} (NGSP) units (14), which allows a comparison of the results from Japanese studies and previous studies from Western countries.

CVD in East Asian people is characterized by a higher rate of stroke and lower rate of coronary heart disease compared with CVD in Western populations (15). In one previous study evaluating the association between HbA_{1c} and incidence of stroke in Japan, ischemic stroke, but not hemorrhagic stroke, was associated with HbA_{1c} in Asian populations (12). Other studies from Japan (11,13) showed a significant association between HbA_{1c} and CVD; however, the number of participants and CVD events were too small to calculate the risk by subtype of CVD, such as coronary heart disease, stroke, cerebral infarction, and cerebral hemorrhage.

The current study was performed to examine the association between HbA_{1c} using NGSP values and the risks for death from all causes and from CVD (coronary

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 HbA$_{1c}$ 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 access 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. HbA$_{1c}$ was measured using the high-performance liquid chromatography method. The range of coefficient of variance of HbA$_{1c}$ measurement in this laboratory was 1.19–1.79% intra-assay and 0.24–0.45% interassay in the 1990s. HbA$_{1c}$ (JDS) values were converted to HbA$_{1c}$ (NGSP) values using the conversion formula provided by JDS: HbA$_{1c}$ NGSP value (%) = 1.02 × JDS value (%) + 0.25 (14). All present analyses adopted the HbA$_{1c}$ 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 I00 to I99 (ICD-10); coronary heart disease, from 410 to 414 (ICD-9) and from I20 to I25 (ICD-10); stroke, from 430 to 438 (ICD-9) and from I60 to I69 (ICD-10); cerebral infarction, 433, 434, 437.8a, and 437.8b (ICD-9) and I63 and I69–3 (ICD-10); cerebral hemorrhage, from 431 to 432 (ICD-9) and I61 and I69.1 (ICD-10).

Statistical analysis

Participants were divided into six groups; five groups of participants without treatment for diabetes according to HbA$_{1c}$ 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 χ^2 test was used to compare characteristics of participants at baseline according to HbA$_{1c}$ 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 HbA$_{1c}$ were calculated for participants without treatment for diabetes. HRs were also calculated separately for each sex, and the interaction between sex and HbA$_{1c}$ on the mortality from each cause of death was calculated. As HbA$_{1c}$ 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/m^2. The mean HbA$_{1c}$ level was 5.3% (34 mmol/mol). Participants with higher HbA$_{1c}$ 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 HbA$_{1c}$ categories are shown in Table 2. The multivariate-adjusted HR for CVD death associated with a 1% increment in HbA$_{1c}$ was 1.32. Relations to HbA$_{1c}$ with CVD death were graded and continuous, and the multivariate-adjusted HR for CVD death in participants with HbA$_{1c}$ 6.0–6.4% (42–47 mmol/mol) was 2.18 (95% CI 1.22–3.87), and that in participants with HbA$_{1c}$ ≥6.5% (48 mmol/mol) was 2.75 (1.43–5.28); both HRs were significantly higher than that in participants with HbA$_{1c}$ <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 HbA$_{1c}$ <5.0% (31 mmol/mol). Similar associations were

observed between HbA_{1c} and death from coronary heart disease and death from cerebral infarction. On the other hand, cerebral hemorrhage was not significantly associated with HbA_{1c}.

When the association was evaluated separately by sex (Table 3), the results were similar between men and women, and no interaction was observed between sex and HbA_{1c} with regard to the association with all-cause death or death from any CVD (P for interactions: 0.283 for all-cause death, 0.405 for CVD death, 0.119 for death from coronary heart disease, 0.709 for death from stroke, 0.880 for death from cerebral infarction, and 0.390 for death from cerebral hemorrhage). The results were similar when the associations were evaluated after excluding those with anemia (Table 3).

CONCLUSIONS—In the present prospective, community-based study in Japan, the HbA_{1c} level in individuals without treatment for diabetes was significantly and positively associated with an increased risk for all-cause mortality and death from CVD. Among CVDs, coronary heart disease and cerebral infarction were associated with HbA_{1c} levels. The multivariate-adjusted HR for death from CVD was significantly higher for the participants with HbA_{1c} >6.0% (42 mmol/mol) compared with HbA_{1c} <5.0% (31 mmol/mol), even though they were not diagnosed as having diabetes based on HbA_{1c} levels.

Since the association between HbA_{1c} and microangiopathy in patients with diabetes was established, HbA_{1c} has been used for not only the determination of glucose control among patients with diabetes but also the diagnosis of diabetes (1). Macrovascular complications are not specific to diabetes, and the association between HbA_{1c} and the risk for CVD has been reported in the general population (3–13) as well as patients with diabetes (25–28). Recent American College of Cardiology Foundation and American Heart Association guidelines indicate that measurement of HbA_{1c} may be reasonable for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (2). However, the association between HbA_{1c} and the risk for CVD has been reported mainly from Western countries. A recent study in Japan found a significant association between HbA_{1c} and the incidence of CVD (13), although the number of participants was small (n = 1,607) and no association between HbA_{1c} and the incidence of myocardial infarction

Table 1—*Baseline characteristics of study participants according to HbA_{1c} levels at baseline: NIPPON DATA90*

Characteristics	Any	HbA_{1c} in participants without treatment for diabetes					Participants with treatment for diabetes	P*
		<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)		
N	7,120	2,143	3,505	964	191	126	191	
Age (years)	52.3 ± 13.6	46.7 ± 12.6	52.9 ± 13.3	58.4 ± 12.7	60.4 ± 12.2	56.0 ± 11.7	62.7 ± 10.5	<0.001
Women	58.4	65.7	58.0	49.8	42.9	46.0	51.3	<0.001
BMI (kg/m^2)	22.9 ± 3.2	22.3 ± 2.8	22.9 ± 3.2	23.6 ± 3.5	23.8 ± 3.6	25.0 ± 4.4	23.5 ± 3.2	<0.001
Systolic blood pressure (mmHg)	135.1 ± 20.6	129.3 ± 19.9	135.4 ± 20.0	140.7 ± 20.4	145.3 ± 19.2	146.7 ± 22.5	146.9 ± 19.2	<0.001
Diastolic blood pressure (mmHg)	81.2 ± 11.9	79.0 ± 11.8	81.7 ± 11.6	83.0 ± 12.3	84.0 ± 12.4	86.7 ± 12.9	82.7 ± 11.2	<0.001
Total cholesterol (mg/dL)	203.0 ± 37.8	191.7 ± 33.4	204.8 ± 36.8	214.9 ± 39.2	218. 5 ± 41.0	223.6 ± 47.8	207. 4 ± 46.7	<0.001
HDL cholesterol (mg/dL)	54.2 ± 15.3	56.4 ± 15.3	54.3 ± 15.3	51.6 ± 14.8	49.1 ± 15.4	47.1 ± 15.1	48.7 ± 12.9	<0.001
Hemoglobin (g/dL)	13.7 ± 1.6	13.6 ± 1.5	13.6 ± 1.6	13.7 ± 1.7	13.8 ± 1.9	14.2 ± 1.9	13.9 ± 1.6	<0.001
Smoking status								<0.001
Never smoker	60.3	67.7	60.1	50.9	46.1	48.4	51.3	
Ex-smoker	11.0	10.4	10.2	12.7	16.8	12.7	18.3	
Current smoker	28.7	21.9	29.7	36.4	37.2	38.9	30.4	
Alcohol consumption								<0.001
Never drinker	68.5	70.8	70.1	62.8	55.0	58.7	62.8	
Ex-drinker	3.0	2.8	2.7	2.6	5.2	4.8	9.4	
Current drinker	28.5	26.4	27.2	34.6	39.8	36.5	27.7	
Regular exercise	19.9	17.5	19.5	23.7	25.7	15.9	32.5	<0.001
Medical treatment for hypertension	12.9	8.3	11.6	18.3	29.8	24.6	38.2	<0.001
Medical treatment for dyslipidemia	2.7	1.4	2.3	3.8	8.9	5.6	12.6	<0.001

Data are means ± SD or percentages. *One-way ANOVA for continuous variables and χ^2 test for categorical variables.

Table 2—*Risk of death according to the baseline HbA$_{1c}$ levels in 7,120 participants: NIPPON DATA90, 1990–2005*

	HbA$_{1c}$ in participants without 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)	Participants with treatment for diabetes	HbA$_{1c}$ 1% increment †
Person-years of follow-up	30,864	49,192	13,123	2,372	1,727	2,327	
All-cause death							
Cases	199	529	211	63	31	71	
Mortality (per 1,000 person-years)	6.4	10.8	16.1	26.6	17.9	30.5	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.04 (0.89–1.23)	1.01 (0.83–1.23)	1.75 (1.32–2.33)	1.61 (1.11–2.36)	1.66 (1.26–2.19)	1.16 (1.05–1.27)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.08 (0.92–1.28)	1.07 (0.88–1.31)	1.95 (1.46–2.61)	1.72 (1.17–2.52)	1.80 (1.37–2.38)	1.20 (1.09–1.32)
Death from CVD							
Cases	44	147	64	17	12	20	
Mortality (per 1,000 person-years)	1.4	3.0	4.9	7.2	6.9	8.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.28 (0.91–1.79)	1.32 (0.89–1.94)	2.11 (1.21–3.70)	2.83 (1.50–5.37)	2.02 (1.19–3.43)	1.29 (1.10–1.52)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.31 (0.93–1.84)	1.38 (0.93–2.04)	2.18 (1.22–3.87)	2.75 (1.43–5.28)	2.04 (1.19–3.50)	1.32 (1.12–1.56)
Death from coronary heart disease							
Cases	9	27	14	2	3	6	
Mortality (per 1,000 person-years)	0.3	0.5	1.1	0.8	1.7	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.20 (0.57–2.56)	1.55 (0.67–3.59)	1.23 (0.27–5.69)	3.45 (0.93–12.7)	3.10 (1.10–8.77)	1.38 (1.01–1.87)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.15 (0.53–2.48)	1.46 (0.62–3.47)	1.11 (0.23–5.31)	3.19 (0.83–12.3)	2.77 (0.95–8.06)	1.40 (1.02–1.92)
Death from stroke							
Cases	20	60	29	9	3	6	
Mortality (per 1,000 person-years)	0.6	1.2	2.2	3.8	1.7	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.14 (0.69–1.89)	1.30 (0.73–2.30)	2.48 (1.13–5.45)	1.58 (0.47–5.31)	1.32 (0.53–3.29)	1.19 (0.90–1.58)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.19 (0.71–1.99)	1.38 (0.76–2.48)	2.74 (1.21–6.18)	1.57 (0.46–5.38)	1.40 (0.55–3.55)	1.20 (0.89–1.60)
Death from cerebral infarction							
Cases	8	42	15	5	2	6	
Mortality (per 1,000 person-years)	0.3	0.9	1.1	2.1	1.2	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.98 (0.93–4.22)	1.58 (0.67–3.74)	3.72 (1.21–11.4)	2.78 (0.59–13.1)	3.26 (1.13–9.41)	1.31 (0.93–1.85)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	2.13 (0.99–4.59)	1.84 (0.76–4.43)	5.28 (1.66–16.8)	3.30 (0.68–15.9)	4.09 (1.38–12.1)	1.38 (0.98–1.92)
Death from cerebral hemorrhage							
Cases	8	8	4	4	1	0	
Mortality (per 1,000 person-years)	0.3	0.2	0.3	1.7	0.6	—	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	0.41 (0.15–1.09)	0.52 (0.16–1.75)	2.82 (0.84–9.42)	1.31 (0.16–10.5)	—	1.01 (0.49–2.04)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	0.44 (0.16–1.18)	0.50 (0.15–1.74)	2.46 (0.69–8.78)	1.29 (0.16–10.7)	—	0.96 (0.45–2.04)

*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.

Table 3—*Multivariate-adjusted HR* of death according to the baseline HbA_{1c} levels in men, women, and participants without anemia: sensitivity analyses, NIPPON DATA90, 1990–2005*

	HbA_{1c} 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.)	1.09 (0.86–1.37)	1.19 (0.90–1.56)	1.96 (1.33–2.88)	1.96 (1.19–3.21)	1.85 (1.28–2.67)
Women (*n* = 4,158)	1.00 (ref.)	1.03 (0.81–1.31)	0.92 (0.68–1.24)	1.94 (1.24–3.05)	1.28 (0.68–2.40)	1.73 (1.14–2.65)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.07 (0.88–1.30)	0.93 (0.73–1.18)	1.67 (1.18–2.39)	1.59 (1.01–2.51)	1.72 (1.24–2.39)
Death from CVD						
Men (*n* = 2,962)	1.00 (ref.)	1.12 (0.69–1.80)	1.17 (0.67–2.05)	1.71 (0.75–3.87)	3.98 (1.81–8.74)	1.86 (0.90–3.88)
Women (*n* = 4,158)	1.00 (ref.)	1.46 (0.89–2.39)	1.51 (0.86–2.67)	2.78 (1.22–6.32)	1.16 (0.27–5.02)	2.21 (0.98–4.96)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.31 (0.88–1.95)	1.10 (0.68–1.77)	1.63 (0.80–3.32)	2.16 (0.97–4.82)	2.03 (1.10–3.75)
Death from coronary heart disease						
Men (*n* = 2,962)	1.00 (ref.)	1.46 (0.48–4.47)	2.71 (0.85–8.65)	1.16 (0.13–10.6)	4.83 (0.83–28.3)	4.37 (1.11–17.2)
Women (*n* = 4,158)	1.00 (ref.)	0.83 (0.29–2.40)	0.32 (0.06–1.73)	0.99 (0.10–9.26)	2.57 (0.29–22.9)	1.00 (0.11–9.11)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	0.99 (0.43–2.28)	1.01 (0.37–2.73)	1.13 (0.23–5.59)	3.16 (0.79–12.7)	2.25 (0.69–7.28)
Death from stroke						
Men (*n* = 2,962)	1.00 (ref.)	0.91 (0.46–1.83)	0.86 (0.37–2.02)	1.75 (0.55–5.64)	2.37 (0.63–8.94)	1.47 (0.46–4.71)
Women (*n* = 4,158)	1.00 (ref.)	1.48 (0.68–3.22)	2.02 (0.85–4.80)	4.39 (1.36–14.2)	—	1.20 (0.25–5.86)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.24 (0.67–2.28)	1.10 (0.53–2.28)	1.40 (0.44–4.42)	1.30 (0.29–5.91)	1.18 (0.38–3.68)
Death from cerebral infarction						
Men (*n* = 2,962)	1.00 (ref.)	1.38 (0.54–3.54)	0.44 (0.11–1.85)	2.05 (0.39–10.7)	3.23 (0.55–19.0)	2.88 (0.77–10.8)
Women (*n* = 4,158)	1.00 (ref.)	3.98 (1.21–25.6)	5.57 (1.21–25.6)	16.5 (2.61–104.1)	—	7.54 (1.02–55.8)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	3.30 (1.15–9.49)	2.20 (0.67–7.26)	3.53 (0.62–20.2)	3.34 (0.36–31.3)	4.83 (1.16–20.1)
Death from cerebral hemorrhage						
Men (*n* = 2,962)	1.00 (ref.)	0.45 (0.11–1.83)	1.11 (0.26–4.72)	1.70 (0.28–10.2)	1.44 (0.14–14.6)	—
Women (*n* = 4,158)	1.00 (ref.)	0.27 (0.06–1.15)	—	2.73 (0.38–19.5)	—	—
Participants without anemia (*n* = 5,978)	1.00 (ref.)	0.22 (0.06–0.77)	0.36 (0.09–1.51)	0.92 (0.17–5.05)	1.00 (0.11–8.78)	—

*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.

was shown owing to the small number of cases. Our results demonstrate that HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 5.0–5.5% (10). The European Prospective Investigation into Cancer (EPIC)-Norfolk study also evaluated the HbA_{1c} categories and CVD death, and relative risk of the participants with HbA_{1c} 5.5–6.9% was ~2.5 compared with the participants with HbA_{1c} <5.0% (3). Thus, the relative strength of the association of HbA_{1c} 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 HbA_{1c} within the nondiabetic range (3–8,10,29). In the current study, participants with HbA_{1c} 6.0–6.4% (42–47 mmol/mol) had a significantly increased risk of death from CVD and cerebral infarction. HbA_{1c} values were more closely related to postprandial hyperglycemia than to fasting glucose levels (30). High-normal HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} and all-cause death and death from CVD were observed in our study. Recently, a J-shape relationship between HbA_{1c} and all-cause mortality was reported in a study of the New Zealand general population (8). Participants with

HbA_{1c} <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 HbA_{1c} 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 HbA_{1c} levels was causal or merely a result of reserve causation due to preexisting disease. In our study, the number of participants with HbA_{1c} <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 HbA_{1c} 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 previous studies in Asian countries were from Japan and used JDS values for HbA_{1c}, whereas our analyses used NGSP values for HbA_{1c}, 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 HbA_{1c}, and our data suggested that HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} at baseline, which might have underestimated the relationship owing to regression dilution bias (38), and changes in HbA_{1c} during the 15-year follow-up period were not taken into account.

In conclusion, HbA_{1c} 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 HbA_{1c} levels of 6.0–6.4% (42–47 mmol/mol), which are below the threshold for diabetes. HbA_{1c} is a useful marker of glucose metabolism for mass screening because fasting is not required for its assessment. Our results showed that HbA_{1c} was associated with CVD death in general East Asian populations, as in Western populations. Further study is needed to establish whether the measurement of HbA_{1c} 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. and H.N. collected data, contributed to discussion, reviewed and edited the manuscript, and approved the final version of the manuscript. H.O. and H.A. contributed to discussion, reviewed and edited the manuscript, and approved the final version of the manuscript. A.K., Y.K., T.H., T.Ohk., A.O., T.Oka., and H.U. collected data, contributed to the discussion, reviewed and edited 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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