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Hemoglobin A_{1c} Levels and the Risk of Cardiovascular Disease in People Without Known Diabetes

A Population-Based Cohort Study in Japan

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Editor: Patricia Zrelak.
Received: January 8, 2015; revised: February 13, 2015; accepted: March 25, 2015.
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Conflict of interest: AG has received a lecture fee from Boehringer Ingelheim, outside of the submitted work. MN received grants from Astra Zeneca K.K., Mitsubishi-Tanabe Pharma Corp., Kowa Pharmaceutical Co. Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., and Kyowa Hakko Kirin Co. Ltd. as well as lecture fees from Sanofi K.K., Mitsubishi Tanabe Pharma Corp., Daiichi Sankyo company, Eli Lilly Japan K.K., MSD K.K., Novo Nordisk Pharma Ltd., Kissei Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Astellas Pharma Inc., Kowa Pharmaceutical Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Meiji Seika Pharma Co. Ltd., and Kyowa Hakko Kirin Co. Ltd., outside of the submitted work. HY has received lecture fees from Merck/MSD, Takeda Pharmaceutical Company Limited, Boehringer Ingelheim, and Hiroshima Prefectural Medical Association, outside of the submitted work. MI is the beneficiary of a financial contribution from the AXA Research Fund as a chair holder on the AXA Department of Health and Human Security, Graduate School of Medicine, The University of Tokyo. The AXA Research Fund had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to publish the results. All other authors declare that they do not have any potential conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000785

Abstract: High hemoglobin A_{1c} (HbA_{1c}) levels are strongly associated with an increased risk of cardiovascular disease (CVD) in people with and without diabetes. However, information regarding the relationship between low HbA_{1c} levels and the risk of CVD among people without known diabetes is limited. The aim of this large-scale, prospective, population-based cohort study was to clarify the association between HbA_{1c} levels and CVD risk among people without known diabetes.

We followed-up 10,980 men and 18,079 women (46–80 years old and free of CVD and cancer at baseline) in the Japan Public Health Center-based Prospective Study. Using Cox models, we estimated the hazard ratios for CVD risk with adjustments for age, sex, geographic areas, body mass index, smoking status, sports and physical exercise, alcohol intake, systolic blood pressure, non-high-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

During the median follow-up of 9.4 years, 935 CVD events (770 strokes and 165 coronary heart diseases) occurred. We observed a nonlinear association between HbA_{1c} levels and CVD risk in participants without known diabetes. Compared with HbA_{1c} levels of 5.0 to 5.4% (31–36 mmol/mol), the hazard ratios for CVD in participants without known diabetes were 1.50 (95% confidence interval: 1.15–1.95), 1.01 (0.85–1.20), 1.04 (0.82–1.32), and 1.77 (1.32–2.38) for HbA_{1c} levels of <5.0% (<31 mmol/mol), 5.5 to 5.9% (37–41 mmol/mol), 6.0 to 6.4% (42–47 mmol/mol), and ≥6.5% (≥48 mmol/mol), respectively (*P* value for nonlinear trend: <0.001). In addition, the hazard ratio for CVD was 1.81 (1.43–2.29) in patients with known diabetes compared with participants with HbA_{1c} levels of 5.0 to 5.4% and without known diabetes. This nonlinear relation persisted after excluding people with kidney dysfunction, liver dysfunction, anemia, body mass index <18.5 kg/m^2, or early events within 3 years of follow-up (*P* value for nonlinear trend: <0.01 for all tests).

In conclusion, both low and high levels of HbA_{1c} were associated with a higher risk of CVD in a Japanese general population without known diabetes.

(*Medicine* 94(17):e785)

Abbreviations: CVD = cardiovascular disease, HbA_{1c} = hemoglobin A_{1c}, JPHC Study = Japan Public Health Center-based Prospective Study.

INTRODUCTION

Although substantial efforts have been made to control major cardiovascular disease (CVD) risk factors (eg, hypertension

and smoking), CVD remains to be the leading cause of death globally.[1–3] Biomarkers, such as hemoglobin A_{1c} (HbA_{1c}), may be useful for identifying people with increased risk of CVD and eventually help reduce the global burden of CVD.[4,5]

It has been well established that high HbA_{1c} levels are strongly associated with a high risk of CVD in people with[6] and without[4,7] diabetes. Accordingly, several researchers have suggested that HbA_{1c} measurement may be useful for identifying people with an increased risk of CVD.[4,7] However, the association between low HbA_{1c} levels and CVD risk is not well understood. In some studies,[8–10] but not all,[6] it has been suggested that patients with type 2 diabetes and low HbA_{1c} levels may have a higher CVD risk, which is consistent with the observation that severe hypoglycemia is associated with an increased CVD risk among patients with type 2 diabetes.[11] However, the association between low HbA_{1c} levels in people without known diabetes and CVD risk remains unknown. Although a possible association between low HbA_{1c} levels and increased mortality in populations without known diabetes has been previously reported,[4,12,13] the biological mechanisms underlying this association are currently unknown.[13–15] Investigating the association between low HbA_{1c} levels and CVD risk may improve our understanding of health risks associated with low HbA_{1c} levels. The aim of this large-scale, prospective, population-based cohort study was to address the question whether low HbA_{1c} levels are associated with a higher CVD risk among people without known diabetes using strictly standardized HbA_{1c} levels and detailed measurements of covariates in a general Japanese population free of CVD and cancer at baseline.

METHODS

Study Design and Population

The Japan Public Health Centre-based Prospective Study (JPHC Study) was initiated in 1990 for cohort I and in 1993 to 1994 for cohort II. All subjects were Japanese inhabitants from 11 public health center areas, and aged 40 to 59 years in 1990 (cohort I) and 40 to 69 years in 1993 (cohort II). Details of the study design have been described elsewhere.[16] The JPHC Diabetes Study, involving HbA_{1c} measurements and an additional questionnaire concerning diabetes and lifestyle, was conducted among JPHC participants at the time of their health check-ups (the first survey in 1998–2000 and the second survey in 2003–2005).[17] Two public health center areas from Tokyo and Osaka were excluded because information regarding the incidence of coronary heart disease and stroke was not available. Therefore, this present study involved subjects from 9 areas (cohort I: 4 areas; cohort II: 5 areas). Individuals who participated in either of the JPHC Diabetes Study surveys were included in the present study. Among the 35,197 participants from the JPHC Diabetes Study, we excluded 1004 and 984 participants with a history of CVD and cancer, respectively, as well as 4150 participants with missing anthropometric or laboratory data. In total, we analyzed data for 29,059 participants. All participants provided written informed consent before participating in this study. The JPHC Diabetes Study was approved by the institutional review board of the National Center for Global Health and Medicine, Japan.

Measurements

Detailed procedures for the HbA_{1c} measurements have been described previously,[17] and these were performed using high-performance liquid chromatography or immunochemical assays. The overall intra-assay coefficient of variation for HbA_{1c} ranged from 0.0 to 3.4%, and the maximal inter-assay coefficient of variation among the various laboratories ranged from 2.2 to 2.8%. The HbA_{1c} measurement methods differed according to the public health center areas, and therefore, HbA_{1c} values were strictly standardized to minimize inter-laboratory variation. For the calibration procedure, standard samples (approved by the Japan Diabetes Society) were provided to each public health center area before the surveys. HbA_{1c} values were converted to National Glycohemoglobin Standardization Program values.[18] Censoring events (which defined the individual's final data point) were defined as the first CVD event, death, change of residence, loss to follow-up, December 31, 2009 (cohort I), or December 31, 2008 (cohort II). For individuals who participated in both surveys of the JPHC Diabetes Study before the censoring events (35.1% of the study population), the average HbA_{1c} levels were used for analyses to capture their long-term exposure.[10] The sensitivity analyses using the time-dependent Cox proportional hazard models to update the HbA_{1c} levels and diabetes status did not materially change the estimates.

Each participant completed a self-administered questionnaire at the 5-year and/or 10-year follow-up of the JPHC Study, which comprised questions regarding previously diagnosed medical conditions, medication, and lifestyle factors, including physical activity, alcohol intake, dietary intake, and smoking.[19] In the present study, we used data from the JPHC Study questionnaire at the time of entry into the JPHC Diabetes Study, except for participants from cohort I who only participated in the second JPHC Diabetes Study survey (10% of the study population). These participants completed the JPHC Study questionnaire 5 years before their entry into the JPHC Diabetes Study, and these data were used in the current analysis. Sensitivity analyses for excluding these participants did not materially change study findings. At the time of the 2 JPHC Diabetes Study surveys, blood pressure, weight, height, hemoglobin, serum creatinine, alanine aminotransferase, and lipid levels were measured. Body mass index was calculated as weight (kg) divided by height squared (m^2).

We defined CVD as either stroke or coronary heart disease, including myocardial infarction or sudden cardiac death. CVD events were documented based on active patient notifications from the local hospitals, hospital record reviews for participants who reported CVD in the follow-up questionnaires, and a review of death certificates.[20] A total of 78 major hospitals capable of treating patients with acute CVD were included in the registry of CVD events within the 9 public health center areas. Overall, 97% of stroke and 92% of myocardial infarction cases in the 9 areas were treated at these registry hospitals. CVD events were included in this study if they occurred between the time of entry into the JPHC Diabetes Study and December 31, 2009 (cohort I) or December 31, 2008 (cohort II). Changes in residential status, including survival status, were identified using the residential registry in each area. During the follow-up period, 1273 (4.4%) participants died, 420 (1.4%) moved out of the study areas, and 28 (0.1%) were lost to follow-up.

Stroke diagnoses were confirmed according to the National Survey of Stroke criteria[21] by the presence of sudden or rapid-onset focal neurological deficits that last >24 h or until death. Strokes were classified according to subtype: hemorrhagic or ischemic (lacunar or nonlacunar).[20] A diagnosis of definite myocardial infarction was confirmed according to the Monitoring Trends and Determinants of Cardiovascular Disease Project

criteria[22] on the basis of typical chest pain and evidence from electrocardiograms and/or cardiac enzyme levels. For cases of typical prolonged chest pain (>20 min) that were not confirmed by electrocardiograms or cardiac enzymes (8.5% of the total myocardial infarctions), a diagnosis of possible myocardial infarction was made, and these cases were included in the myocardial infarction cases. Sensitivity analyses for excluding cases with possible myocardial infarction did not materially change the findings. In the absence of myocardial infarction diagnoses, deaths that occurred within 1 h from symptom onset were considered as sudden cardiac deaths. Only the first CVD event during the follow-up was included in the analysis; recurrent events were excluded.

Statistical Methods

We followed-up 29,059 participants (46–80 years old) and calculated their person-years from the time of entry into the JPHC Diabetes Study until their censoring event. If individuals participated in both JPHC Diabetes Study surveys, the time of entry at the first survey was considered the starting point. We also calculated the baseline characteristics for patients with diabetes and 5 groups of people without known diabetes categorized by their HbA_{1c} levels: <5.0% (<31 mmol/mol), 5.0 to 5.4% (31–36 mmol/mol), 5.5 to 5.9% (37–41 mmol/mol), 6.0 to 6.4% (42–47 mmol/mol), and ≥6.5% (≥48 mmol/mol). We defined participants as having known diabetes if they had self-reported diabetes or were receiving treatment for diabetes. Following conventional practice,[4] the HbA_{1c} category of 5.0 to 5.4% (31–36 mmol/mol) was used as the reference category.

To examine the CVD risk in the 6 groups of people, we used Cox proportional hazards models and estimated the hazard ratios and 95% confidence intervals (categorical models). These models were adjusted for age, sex, health center areas, body mass index, smoking status (never smoked, past smoker, or current smoker), alcohol intake (current nondrinker, occasional drinker, or current drinker), sports and physical exercise (≥1 day/week or other), systolic blood pressure (mmHg), high-density lipoprotein cholesterol levels (mmol/L), and non-high-density lipoprotein cholesterol levels (mmol/L). Slightly different physical activity questionnaires were used during the 5-year and 10-year follow-ups of the JPHC Study. Therefore, we first calculated separate estimates for participants who completed the 5-year follow-up questionnaire and for those who completed the 10-year follow-up questionnaire. Because there was no apparent difference in the estimates between these 2 groups, we computed the pooled results using the fixed-effects model with inverse variance weighting.[23]

Among the participants without known diabetes, we computed 2-sided *P* values for linear trends by assigning a mean HbA_{1c} value for each category and including the variables as continuous variables in the models. We also computed 2-sided *P* values for quadratic trends (*P* value for quadratic trend) by including a quadratic term in each linear trend model. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals[24] and found to be appropriate. For sensitivity analysis, we further examined the association between HbA_{1c} levels and CVD after excluding people with kidney dysfunction (estimated glomerular filtration < 60.0 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$),[25] liver dysfunction (alanine aminotransferase ≥100 IU/L), anemia (hemoglobin < 100 g/L), or low body mass index (<18.5 kg/m^2). Further analyses were also conducted after excluding CVD cases with an early diagnosis (within 3 years of follow-up) from both the numerator and denominator (278 participants). To examine the shape of the association between continuous HbA_{1c} levels and CVD risk among people without known diabetes, we fitted restricted cubic spline models by including transformed variables of HbA_{1c} levels in the Cox models, with adjustment for the same covariates that were used in the categorical models. We fitted the models using 3, 4, and 5 knots at percentiles, and chose the number of knots that produced the smallest Akaike Information Criterion. The level of significance was set at *P* value < 0.05. Analyses were performed using Stata version 12.1 (StataCorp, College Station, TX).

RESULTS

The baseline characteristics of the study population according to the 6 groups are shown in Table 1. Compared with participants with lower HbA_{1c} levels, participants with higher HbA_{1c} levels or known diabetes tended to be older; current or past smokers; have a higher body mass index, blood pressure, and non-high-density lipoprotein cholesterol levels; have lower high-density lipoprotein cholesterol levels; use lipid-lowering medication(s); be engaged in physical activity; and consume more calories.

During the median follow-up of 9.4 years (238,456 person-years), 770 strokes (226 lacunar infarctions, 232 nonlacunar infarctions, 311 hemorrhagic strokes, and 1 stroke of undetermined type) and 165 coronary heart diseases (129 definite myocardial infarctions, 12 possible myocardial infarctions, and 24 sudden cardiac deaths) were documented. Table 2 shows the associations for CVD, coronary heart disease, and stroke risk in the 6 groups. After multivariable adjustment for potential confounding factors, we observed a nonlinear relation between HbA_{1c} levels and CVD risk (model 2; *P* value for quadratic trend: <0.001). The nonlinear trend was observed even after excluding people with kidney dysfunction, liver dysfunction, anemia, and low body mass index (*P* value for quadratic trend: <0.05 for all tests). Further adjustment for the use of lipid-lowering medication(s) or total energy intake resulted in similar results (*P* value for quadratic trend: <0.001 for all tests, data not shown). Similar findings were observed when CVD cases with an early diagnosis (within 3 years of follow-up) were excluded (*P* value for quadratic trend: 0.002). Spline curves indicated a U-shaped relation, with increased CVD risk observed in participants with low and high levels of HbA_{1c} (Figure 1A). A similar pattern was observed for stroke risk (Table 2, Figure 1B). Because nonlinear associations were observed, particularly for stroke, we further examined the association between HbA_{1c} levels and stroke subtypes. We observed nonlinear trends for the risks of hemorrhagic and nonlacunar ischemic stroke (model 2; *P* values for quadratic trend: 0.018 and 0.006, respectively), and a similar pattern was suggested for lacunar stroke (model 2; *P* value for quadratic trend: 0.066). Participants with high HbA_{1c} levels (≥6.5%, ≥48 mmol/mol) or known diabetes had an increased risk of ischemic stroke (both lacunar and nonlacunar; model 2). A linear relation was suggested for coronary heart disease risk (Table 2, Figure 1C), although the number of coronary heart disease cases was likely too small to examine its risk in participants with low HbA_{1c} levels. Participants with known diabetes had increased risks of CVD, stroke, and coronary heart disease (model 2).

Stratified analysis according to sex suggested an increased CVD risk existed in men with low and high levels of HbA_{1c} (Table 3). Among women, increased CVD risk was apparent in

TABLE 1. Baseline Characteristics According to Hemoglobin A_{1c} Levels and Known Diabetes

Characteristic	HbA_{1c} Levels in Participants Without Known Diabetes					Known Diabetes
	<5.0% (<31 mmol/mol) N = 2008	5.0–5.4% (31–36 mmol/mol) N = 8177	5.5–5.9% (37–41 mmol/mol) N = 12,450	6.0–6.4% (42–47 mmol/mol) N = 3635	≥6.5% (≥48 mmol/mol) N = 1009	N = 1780
HbA_{1c}, %	4.8 ± 0.2	5.2 ± 0.1	5.7 ± 0.1	6.1 ± 0.1	7.1 ± 0.9	7.0 ± 1.3
Age, years	61.5 ± 8.1	62.1 ± 7.3	62.8 ± 6.6	63.3 ± 6.4	63.5 ± 6.5	64.2 ± 6.4
Men*, %	43.2	36.3	34.5	39.5	47.6	51.3
Body mass index*, kg/m^2	23.4 ± 3.1	23.4 ± 3.1	23.7 ± 3.1	24.3 ± 3.3	25.0 ± 3.6	24.3 ± 3.4
Diabetes treatment, %						64.1
No medication, %						46.1
Oral hypoglycemic agent only, %						47.4
Insulin, %						6.5
Current smoking*, %	13.9	12.8	14.6	18.8	25.1	19.2
Past smoking*, %	10.1	9.7	10.4	11.8	12.6	15.1
Sports and physical exercise*, ≥1 day/week, %	34.8	40.7	46.5	48.1	50.3	48.9
Current alcohol drinking*, %	35.6	31.7	30.2	34.6	39.3	37.2
Ethanol intake*, g/week	5 (0–190)	6 (0–161)	16 (0–162)	42 (1–252)	78 (1–262)	40 (1–252)
Systolic blood pressure*, mmHg	130 ± 17	130 ± 17	130 ± 17	132 ± 17	135 ± 18	133 ± 17
Diastolic blood pressure*, mmHg	77 ± 11	77 ± 11	78 ± 10	79 ± 11	79 ± 11	77 ± 10
Non-high-density lipoprotein cholesterol*, mmol/L	3.52 ± 0.85	3.75 ± 0.84	3.92 ± 0.85	4.01 ± 0.88	4.13 ± 0.95	3.89 ± 0.89
High-density lipoprotein cholesterol*, mmol/L	1.53 ± 0.39	1.55 ± 0.39	1.52 ± 0.38	1.49 ± 0.38	1.41 ± 0.35	1.45 ± 0.39
Lipid-lowering medication use*, %	3.3	5.9	8.8	11.6	12.3	13.1
Total energy*, kcal/day	1865 (1471–2401)	1926 (1530–2420)	1970 (1564–2468)	1987 (1597–2497)	2027 (1615–2532)	1891 (1505–2382)

Data are presented as mean ± standard deviation, percentage, or median (interquartile range). HbA_{1c} = hemoglobin A_{1c}.
* All variables (with the exception of age and HbA_{1c}) were adjusted for age.

TABLE 2. Incidence of Cardiovascular Disease According to Hemoglobin A_{1c} Levels and Known Diabetes

		HbA_{1c} Levels in Participants Without Known Diabetes							Known Diabetes
		<5.0% (<31 mmol/mol) N = 2008	5.0–5.4% (31–36 mmol/mol) N = 8177	5.5–5.9% (37–41 mmol/mol) N = 12,450	6.0–6.4% (42–47 mmol/mol) N = 3635	≥6.5% (≥48 mmol/mol) N = 1009	*P* for Linear Trend	*P* for Quadratic Trend	N = 1780
	Person-years	17,043	70,311	101,292	28,226	7700			13,885
Cardiovascular disease	No. of events	80	228	352	108	60			107
	Crude incidence rate*	7.7	3.2	3.5	3.8	7.8			7.7
	Model 1	1.46 (1.13–1.90)	1.00	1.05 (0.89–1.25)	1.13 (0.89–1.43)	2.10 (1.57–2.81)	0.005	< 0 .001	1.92 (1.52–2.42)
	Model 2	1.50 (1.15–1.95)	1.00	1.01 (0.85–1.20)	1.04 (0.82–1.32)	1.77 (1.32–2.38)	0.069	< 0.001	1.81 (1.43–2.29)
	Model 2 + excluding participants with kidney dysfunction	1.49 (0.997–2.22)	1.00	1.03 (0.79–1.34)	1.05 (0.73–1.51)	2.18 (1.39–3.42)	0.10	0.001	1.37 (0.92–2.03)
	Model 2 + excluding participants with liver dysfunction	1.48 (1.13–1.92)	1.00	1.00 (0.84–1.19)	1.04 (0.82–1.32)	1.80 (1.34–2.41)	0.053	< 0.001	1.78 (1.41–2.26)
	Model 2 + excluding participants with anemia	1.50 (1.15–1.95)	1.00	1.00 (0.84–1.19)	1.03 (0.81–1.31)	1.73 (1.28–2.33)	0.099	< 0.001	1.81 (1.43–2.28)
	Model 2 + excluding participants with low body mass index	1.51 (1.15–1.97)	1.00	1.01 (0.84–1.20)	1.04 (0.81–1.32)	1.77 (1.31–2.39)	0.069	< 0.001	1.83 (1.45–2.32)
	Model 2 + excluding early diagnosis cases	1.53 (1.12–2.10)	1.00	1.11 (0.90–1.36)	1.33 (1.01–1.75)	2.07 (1.45–2.94)	0.004	0.002	1.83 (1.37–2.44)
Stroke	No. of events	71	193	288	83	49			86
	Crude incidence rate*	4.2	2.7	2.8	2.9	6.4			6.2
	Model 1	1.55 (1.17–2.05)	1.00	1.02 (0.84–1.22)	1.03 (0.79–1.34)	2.06 (1.49–2.85)	0.072	< 0.001	1.84 (1.43–2.38)
	Model 2	1.55 (1.17–2.05)	1.00	0.99 (0.82–1.20)	0.97 (0.74–1.26)	1.80 (1.30–2.50)	0.24	< 0.001	1.79 (1.38–2.31)
Hemorrhagic stroke	No. of events	33	85	125	32	13			23
	Crude incidence rate*	1.9	1.2	1.2	1.1	1.7			1.7
	Model 1	1.74 (1.15–2.62)	1.00	0.98 (0.74–1.30)	0.89 (0.59–1.35)	1.26 (0.70–2.27)	0.31	0.010	1.22 (0.76–1.95)
	Model 2	1.72 (1.14–2.60)	1.00	0.97 (0.73–1.29)	0.87 (0.57–1.32)	1.15 (0.63–2.09)	0.27	0.018	1.23 (0.76–1.97)
Ischemic stroke	No. of events	38	108	162	51	36			63
	Crude incidence rate*	2.2	1.5	1.6	1.8	4.7			4.5
	Model 1	1.45 (0.99–2.13)	1.00	1.04 (0.81–1.34)	1.15 (0.81–1.34)	2.72 (1.83–4.04)	< 0.001	< 0.001	2.31 (1.69–3.17)
	Model 2	1.47 (0.996–2.15)	1.00	1.00 (0.78–1.29)	1.06 (0.75–1.51)	2.29 (1.53–3.42)	0.011	< 0.001	2.19 (1.60–3.00)
Lacunar stroke	No. of events	18	53	77	27	17			34
	Crude incidence rate*	1.1	0.8	0.8	1.0	2.2			2.4
	Model 1	1.40 (0.81–2.44)	1.00	0.98 (0.68–1.41)	1.21 (0.74–1.97)	2.81 (1.55–5.09)	0.014	0.052	2.52 (1.63–3.89)
	Model 2	1.41 (0.81–2.46)	1.00	0.94 (0.65–1.35)	1.10 (0.68–1.80)	2.21 (1.20–4.06)	0.067	0.066	2.38 (1.54–3.68)
Nonlacunar ischemic stroke	No. of events	20	55	85	24	19			29

		HbA_{1c} Levels in Participants Without Known Diabetes							Known 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)	*P* for Linear Trend	*P* for Quadratic Trend	
		N = 2008	N = 8177	N = 12,450	N = 3635	N = 1009			N = 1780
Coronary heart disease	Crude incidence rate*	1.2	0.8	0.8	0.9	2.5			2.1
	Model 1	1.50 (0.88–2.56)	1.00	1.10 (0.78–1.56)	1.08 (0.66–1.78)	2.81 (1.65–4.79)	0.018	0.005	2.09 (1.33–3.30)
	Model 2	1.51 (0.89–2.58)	1.00	1.07 (0.75–1.52)	1.02 (0.62–1.69)	2.47 (1.43–4.25)	0.066	0.006	1.99 (1.26–3.16)
	No. of events	9	35	64	25	11			21
Cardiovascular disease	Crude incidence rate*	0.5	0.5	0.6	0.9	1.4			1.5
	Model 1	1.07 (0.50–2.30)	1.00	1.26 (0.82–1.92)	1.69 (0.997–2.88)	2.56 (1.29–5.07)	0.004	0.82	2.23 (1.33–4.06)
	Model 2	1.23 (0.57–2.56)	1.00	1.09 (0.71–1.67)	1.42 (0.83–2.43)	1.92 (0.96–3.85)	0.046	0.61	1.94 (1.11–3.41)

Model 1 was adjusted for age, sex, and public health center areas. Model 2 was further adjusted for body mass index, smoking status, sports and physical exercise, alcohol intake, systolic blood pressure, non-high-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Data are presented as hazard ratios (95% confidence interval) unless otherwise indicated. HbA_{1c} = hemoglobin A_{1c}.

* Crude incidence rate per 1000 person-years.

FIGURE 1. Hazard ratios for cardiovascular events according to continuous hemoglobin A_{1c} (HbA_{1c}) levels among participants without known diabetes. Restricted cubic spline models with the inclusion of transformed variables in the Cox model were used to estimate hazard ratios (solid curve) with point-wise 95% confidence intervals (grey shaded area) for (A) cardiovascular disease, (B) stroke, and (C) coronary heart disease. An HbA_{1c} level of 5.3% (ie, the mean HbA_{1c} level in people with HbA_{1c} levels of 5.0–5.5%) was used to estimate all hazard ratios. We chose the number of knots that produced the smallest Akaike Information Criterion. Hazard ratios were adjusted for age, sex, public health center areas, body mass index, smoking status, alcohol intake, sports and physical exercise, systolic blood pressure, non-high-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

TABLE 3. Sex-Stratified Incidence of Cardiovascular Disease According to Hemoglobin A_{1c} Levels and Known Diabetes

	HbA_{1c} Levels in Participants Without Known Diabetes							Known 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)	*P* for Linear Trend	*P* for Quadratic Trend	
Men	**N = 855**	**N = 2946**	**N = 4312**	**N = 1452**	**N = 485**			**N = 930**
Person-years	6948	24,567	33,882	11,065	3539			7037
No. of events	58	113	167	63	36			75
Crude incidence rate*	8.3	4.6	4.9	5.7	10.2			10.7
Model 1	1.89 (1.36–2.63)	1.00	1.08 (0.84–1.37)	1.32 (0.96–1.80)	2.21 (1.50–3.27)	0.046	<0.001	2.16 (1.61–2.91)
Model 2	1.95 (1.40–2.71)	1.00	1.02 (0.80–1.30)	1.20 (0.87–1.65)	1.83 (1.23–2.73)	0.22	<0.001	2.06 (1.53–2.79)
Women	**N = 1153**	**N = 5231**	**N = 8138**	**N = 2183**	**N = 524**			**N = 850**
Person-years	10,095	45,744	67,410	17,160	4161			6848
No. of events	22	115	185	45	24			32
Crude incidence rate*	2.2	2.5	2.7	2.6	5.8			4.7
Model 1	0.93 (0.58–1.47)	1.00	1.02 (0.80–1.34)	0.93 (0.65–1.33)	2.06 (1.32–3.21)	0.032	0.048	1.60 (1.08–2.37)
Model 2	0.94 (0.59–1.50)	1.00	0.99 (0.78–1.26)	0.87 (0.61–1.25)	1.82 (1.16–2.85)	0.12	0.049	1.50 (1.01–2.22)

Model 1 was adjusted for age and public health center areas. Model 2 was further adjusted for body mass index, smoking status, sports and physical exercise, alcohol intake, systolic blood pressure, non-high-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Data are presented as hazard ratios (95% confidence interval) unless otherwise indicated. HbA_{1c} = hemoglobin A_{1c}.

* Crude incidence rate per 1000 person-years.

those with HbA_{1c} levels of ≥6.5% (≥48 mmol/mol) or known diabetes.

DISCUSSION

In this large-scale, prospective, cohort study in a general Japanese population, both low and high levels of HbA_{1c} were associated with an increased risk of CVD among participants without known diabetes. The nonlinear association between HbA_{1c} levels and CVD risk persisted even after excluding participants with kidney dysfunction, liver dysfunction, anemia, and low body mass index. Furthermore, the patterns of the association between low HbA_{1c} levels and each CVD subset differed from that for diabetes or high HbA_{1c} levels. Low HbA_{1c} levels were associated with an increased risk of stroke, especially hemorrhagic stroke, while diabetes and high HbA_{1c} levels were associated with increased risks of coronary heart disease and stroke, especially ischemic stroke. The observed CVD risk in individuals with diabetes in this study was also consistent with accumulating evidence of diabetes as a risk factor for CVD.[26,27] These findings emphasize a possible increased CVD risk among people without known diabetes and with low HbA_{1c} levels.

The observed CVD risk among people with low HbA_{1c} levels and no known diabetes is particularly important, because this increased risk could not be related to hypoglycemia[11] induced by diabetes treatment. Although a possible increased CVD risk or low HbA_{1c} levels among people without known diabetes have been suggested,[4,13,28] most studies did not find a statistically significant association.[4,13] However, we found a significant association between low HbA_{1c} levels and CVD, particularly stroke, possibly because of a sufficient number of stroke events in this study. Earlier studies were limited by small sample sizes and HbA_{1c} measurements that were obtained from frozen whole blood samples that were stored for >10 years.[4,13] A significant nonlinear association between HbA_{1c} levels and CVD risk among people without known diabetes has been reported in a recent pooled analysis; however, the lack of assay standardization and the significant heterogeneity between assay characteristics for HbA_{1c} measurements may have limited the interpretation of the results.[28] As previously shown, low HbA_{1c} levels are associated with increased all-cause mortality in people without diabetes.[4,12,13] According to our findings, the elevated incidence of CVD may partially explain the increased mortality among people with low HbA_{1c} levels. HbA_{1c} level is increasingly being used to screen for diabetes and therefore, our findings may facilitate the interpretation of low HbA_{1c} levels in the nondiabetic population.

We were also able to confirm that HbA_{1c} levels of ≥6.5% (≥48 mmol/mol) in people without known diabetes were associated with an increased CVD risk, which was consistent with other studies that were conducted in Japan[7,29,30] and other countries.[4,8] Although a significantly increased CVD risk was not observed for the groups with elevated HbA_{1c} levels in the nondiabetic range, the spline analyses (Figure 1A) appeared to suggest a positive linear association between continuous HbA_{1c} levels and CVD risk in those with HbA_{1c} levels of ≥5.5% (≥37 mmol/mol). Earlier investigators have also documented an increased CVD risk with increasing HbA_{1c} levels within the nondiabetic range.[4,7,29,31] Furthermore, individuals with prediabetes (defined by glucose levels during oral glucose tolerance tests) may have a 20% increased risk of CVD, compared to those with normal glycemia according to recent meta-analyses.[32,33] Therefore, hyperglycemia within the nondiabetic range may be associated with an increased CVD risk in a continuous manner.

The mechanisms responsible for the observed association between low HbA_{1c} levels and increased CVD risk among people without known diabetes remain largely unknown. In addition, it is unknown whether low blood glucose levels not induced by diabetes treatment could have a direct effect on blood vessels. We observed similar results (data not shown) when we adjusted for casual blood glucose levels, which suggested that the association between low HbA_{1c} levels and increased CVD risk may not be explained by blood glucose levels. Abnormal red-cell turnover, which can lead to low HbA_{1c} levels,[13] might explain the association. However, the association persisted after we excluded participants with factors that affect red-cell turnover, including kidney dysfunction, liver dysfunction, and anemia. Alternatively, chronic inadequate nutrition may explain the possible increased risk among people with low HbA_{1c} levels. However, the total energy intake did not indicate inadequate nutrition in participants with HbA_{1c} levels of <5.0% (<31 mmol/mol), and adjustment for total energy intake did not change the results. Further, excluding people with a low body mass index at baseline provided similar results. Therefore, confounding by these factors alone may not explain the observed association. Although the biological mechanisms underlying this association remain unresolved, our data support the notion that low HbA_{1c} levels may be a marker for identifying people who are at increased risk of CVD.[13] In addition, based on our findings, diabetic patients with low HbA_{1c} levels (eg, <5.0%, <31 mmol/mol) may have an increased risk of CVD, possibly due to glycemic and nonglycemic factors.

This study has several strengths. First, we strictly standardized the HbA_{1c} values using approved standard samples to reduce the possibility of measurement error, leading to less biased estimates. Second, the use of a population-based prospective cohort design with low loss to follow-up and a large sample size should minimize the possibility of selection bias. Third, the systematic surveys of CVD events likely reduced outcome misclassification in our study. Finally, we were able to examine the relation between HbA_{1c} levels and stroke subtypes because of the large number of stroke events.

Despite these strengths, certain limitations of the present study merit consideration. First, HbA_{1c} levels and diabetes status may have changed during the follow-up, but only single measurements of HbA_{1c} were available for most participants (65%). If HbA_{1c} levels during the follow-up had been available for all participants, the association between HbA_{1c} and CVD risk would likely have been stronger. Second, the increased CVD risk observed in individuals with low HbA_{1c} levels may not necessarily indicate a causal association. Third, information regarding socioeconomic status was not available, which might explain the increased CVD risk among people with low HbA_{1c} levels. However, there is no clear evidence that people with low socioeconomic status have low HbA_{1c} levels. Fourth, we could not consider the genetic background of our participants because genetic variants linked to CVD or risk factors (eg, hypertension[34]) were not measured in our study. However, it is unlikely that the missing information on such variants would bias the association between HbA_{1c} levels and CVD risk because such variants do not tend to affect HbA_{1c} levels. Finally, our results may not be applicable to other populations, especially Western populations, because East Asians tend to have a higher incidence of stroke and lower incidence of coronary heart disease compared with those in Western populations.[35] Therefore, the nonlinear relation between HbA_{1c} and stroke might be especially relevant to Asians.

In conclusion, both low and high levels of HbA_{1c} were associated with a higher risk of CVD in a general Japanese population without known diabetes. These data support the notion that very low and high HbA_{1c} levels may be markers for identifying people with an increased health risk.

ACKNOWLEDGMENTS

We thank all the staff members in each study area and in the central and cardiovascular offices for their cooperation and technical assistance. We also thank Hadrien Charvat at the Epidemiology and Prevention Group, Research Center for Cancer Prevention and Screening, National Cancer Center for providing statistical advice.

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FUNDING: This study was supported by Grants-in-Aid for Cancer Research and for the Third Term Comprehensive Control Research for Cancer and Health Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan (Research on Health Services H10–074, Medical Frontier Strategy Research H13–008, Clinical Research for Evidence-based Medicine H14–008 and H15–006, and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus H16–019, H17–019, H18–028, H19–016, and H25–016). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to publish the results.

OTHER INFORMATION: CONTRIBUTORS: AG analyzed data, drafted the manuscript, reviewed and edited the manuscript, and contributed to discussion. MN and ST conducted, designed, and supervised the study, and contributed to discussion. YM analyzed data and contributed to discussion. MG analyzed data, reviewed and edited the manuscript, and contributed to discussion. MK, AI, TM, MI, and TK conducted the research. YT, KY, IS, YK, and NS conducted the research and contributed to discussion. KK, SO, and AN contributed to discussion. HY reviewed and edited the manuscript, and contributed to discussion. All authors have read and approved the final manuscript.

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