Relationship between HbA1c and risk of retinal hemorrhage in the Japanese general population: the Circulatory Risk in Communities Study (CIRCS)

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ABSTRACT

Aims

Retinal hemorrhage is an important finding on fundus photography. Diabetes mellitus is a cause of retinal hemorrhage, although other causes exist. We sought to better characterize the association between retinal hemorrhage and HbA1c in the Japanese population.

Methods

We conducted a prospective study of 11,644 Japanese men and women aged 30–78 years between 2001 and 2011. Fundus photography was performed as part of an annual cardiovascular disease risk survey. HbA1c was determined by the latex coagulation method throughout the study. We used logistic regression models to examine the association between HbA1c and the risk of retinal hemorrhage and diabetic retinal hemorrhage.

Results

During a median follow-up period of 4.6 years, 509 retinal hemorrhages, including 96 diabetic retinal hemorrhages, were diagnosed. HbA1c was positively associated with the risk of retinal hemorrhage and diabetic retinal hemorrhage among subjects not taking medication for diabetes mellitus at baseline, but not among subjects who were taking medication at baseline.

Conclusions

HbA1c was positively associated with the risk of retinal hemorrhage and the subcategory of diabetic retinal hemorrhage among subjects not taking medication for diabetes mellitus at baseline. The association was evident for diabetic retinal hemorrhage, compared with retinal hemorrhage.

Keywords

prospective study, general population, retinal hemorrhage, HbA1c, diabetes mellitus

1. Introduction

Retinal hemorrhage is an important finding on fundus photography, because severe retinal hemorrhage may damage retinal tissue and impair vision. Diabetes mellitus is a well-known cause of retinal hemorrhage, but the association between diabetes mellitus and the risk of retinal hemorrhage is unclear. Epidemiological studies have examined the association between hemoglobin A1c (HbA1c), hemoglobinA1, plasma glucose level and duration of diabetes mellitus and the risk of diabetic retinopathy, which includes retinal hemorrhage (1-5). However, these studies did not specifically focus on retinal hemorrhage.

The aim of the present study was to investigate the association between HbA1c and the risk of retinal hemorrhage in order to develop prevention strategies for retinal hemorrhage at the population level. We included all retinal hemorrhages and retinal hemorrhages suspected to be caused by diabetes mellitus (diabetic retinal hemorrhage) as outcomes. We also investigated the association between cardiovascular risk factors and the risk of retinal hemorrhage. We analyzed the data from annual health check-ups for Japanese residents and workers.

2. Material and Methods

2.1 Study subjects

Study subjects consisted of Japanese residents and workers between 30 and 78 years of age (mean age; 49.0 years). The residents were from two communities that participated in the Circulatory Risk in Community Study (CIRCS) (6) in Ikawa, Akita Prefecture and the Minami-Takayasu district of Yao city, Osaka Prefecture. The workers were employees of 20 companies in Osaka Prefecture. At baseline, there were 18,478 subjects, including 7,020 residents and 11,458 workers. We excluded 1,100 subjects who did not undergo fundus photography and 160 individuals who were diagnosed with retinal hemorrhage caused by diabetes mellitus or hypertension at the time of the first cardiovascular disease risk survey. HbA1c was not determined in 39 subjects, who were also excluded from the analysis. In addition, 4,618 subjects were excluded because they only underwent a single health check-up. Of the remaining 12,561 subjects, we used the data from 11,644 subjects (6,999 males and 4,645 females; 4,834 residents and 6,810 workers) (Supplemental Table 1) who had complete information on Scott classification for diabetic retinopathy, Scheie classification for hypertensive retinopathy, and accessory information about spot bleeding, retinal vein occlusion, etc. The study was approved by the ethics committee of the Osaka Medical Center for Health Science and Promotion.

2.2 Risk factor survey

Annual cardiovascular disease risk surveys were performed from July 2001 to February 2011. Fundus photography with digital image storage was conducted during the study period based on the following criteria. In workers, a single eye, usually the right eye, was examined with fundus photography annually. Subjects diagnosed with diabetes mellitus during the previous survey underwent annual fundus photography of both eyes. Subjects with any retinal

hemorrhage during the previous 3 years also underwent fundus photography of both eyes. Residents underwent fundus photography of a single eye, usually the right eye, biennially. Subjects diagnosed with hyperglycemia or hypertension during the previous survey underwent annual fundus photography of a single eye, usually the right eye. Subjects with retinal changes related to hypertension, atherosclerosis, or diabetes mellitus during the previous survey also underwent annual fundus photography of a single eye, usually the right eye. Subjects diagnosed with diabetes mellitus during the previous survey underwent annual fundus photography of both eyes. Subjects with any retinal hemorrhage during the previous 3 years also underwent fundus photography of both eyes. Fundus photography for the right eye represented 98% of single-eye examinations. We used the data from one eye for analysis. In subjects who underwent fundus photography of both eyes, we used information from the right eye only.

Fundus photography was performed using a digital camera (CR6-45NM, Canon Inc., Tokyo, Japan). Well-trained physicians evaluated the photographs displayed on a 14–15 inch monitor. When physicians identified a new hemorrhage in the retina during the follow-up period, they checked blood test data and medical history. When subjects with retinal hemorrhage met the following criteria, they were considered to have diabetic retinal hemorrhage: borderline to high blood glucose (fasting glucose >110 mg/dL or non-fasting glucose) >140 mg/dL, high HbA1c (HbA1c ≥6.0%, Japan Diabetes Society [JDS] value equivalent to a National Glycohemoglobin Standardization Program [NGSP] value of 6.4%), or medication for diabetes mellitus at time of the survey when retinal hemorrhage was diagnosed. We defined retinal hemorrhage that did not meet these criteria as non-diabetic retinal hemorrhage. We used the Scott classification to evaluate the severity of diabetic retinal hemorrhage (7). Medical technologists also verified the presence of hemorrhages in the

photographs. The final diagnosis of all retinal hemorrhages was based on consensus between the physicians and medical technologists.

HbA1c was determined using the latex coagulation method (AU2700, Olympus Corp., Tokyo, Japan) at the Osaka Medical Center for Health Science and Promotion. We used the following formula to calculate the NGSP HbA1c value based on the JDS value stored in our database: HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25% (8). The HbA1c values reported in the present study are the calculated NGSP values.

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Weight was determined with subjects wearing light clothing. Height was determined with subjects in their socks. Well-trained observers monitored arterial systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) using a standard mercury sphygmomanometer on the right arm after at least 5 minutes of rest. Subjects were interviewed to determine their alcohol use and categorized as never, past, or current drinkers. Smoking habit was also determined during the interview, and subjects were categorized as never, past, or current smokers. Any history of diabetes mellitus, hypertension, cardiovascular disease, and medication use were assessed similarly.

2.3 Statistical Analysis

The follow-up period extended from the day of the first cardiovascular disease risk survey (baseline survey) to the day of the endpoint survey. For subjects diagnosed with retinal hemorrhage, we defined the endpoint survey as the survey in which the subject was first diagnosed with retinal hemorrhage. For subjects who did not develop retinal hemorrhage, we defined the endpoint as the final survey. The follow-up period ranged from 0.3 to 9.1 years (median, 4.6 years).

Subjects were stratified into two groups according to the use of medication for diabetes mellitus at baseline. Subjects were also divided into five categories according to their HbA1c level during the baseline survey: <5.7%, ≥5.7 to <6.5%, ≥6.5 to <7.3%, ≥7.3 to <8.1%, and ≥8.1%. Age- and sex-adjusted mean and proportion values of confounding variables according to HbA1c categories were calculated by analysis of covariance. Odds ratios (ORs) adjusted for age, sex, and multiple variables, respectively, and corresponding 95% confidence intervals (95% CIs) were also determined for the incidence of retinal hemorrhage and diabetic retinal hemorrhage using logistic regression. While calculating ORs, subjects with HbA1c <5.7% at baseline were used as the referent group. We considered the following as confounding variables: baseline age; sex; BMI; current alcohol use (yes or no); current smoking (yes or no); hypertension (SBP ≥140 mmHg, DBP ≥90 mmHg or on anti-hypertensive therapy); serum low-density lipoprotein (LDL) cholesterol level (10 mg/dL); serum high-density lipoprotein (HDL) cholesterol level (10 mg/dL); and initiation of medication for diabetes mellitus, hypertension, and hypercholesterolemia after the baseline survey (yes or no). We also investigated the relationship between confounding variables and the risk of retinal hemorrhage. When we tested the interaction between HbA1c and sex and subject background (resident or worker) status using an interaction term generated by multiplying HbA1c as a continuous variable with either sex or subject background status, we found no significant relationships. We present the combined data (*P* for interaction=0.45 for sex, *P* for interaction=0.14 for background status).

SAS software (version 9.3, SAS Institute Inc., Cary, NC) was used for all analyses. Two-sided *P* values < 0.05 were considered statistically significant and *P* values between 0.05 and 0.10 inclusive were considered borderline significant.

3. Results

During a median follow-up period of 4.6 years for 11,644 subjects, 509 cases of retinal hemorrhage were diagnosed, including 96 cases of diabetic retinal hemorrhage. Table 1 shows the number of cases stratified by use of medication for diabetes mellitus at baseline. The median follow-up for subjects who developed retinal hemorrhage was 3.1 years, compared to 4.8 years for those who did not have retinal hemorrhage.

Table 2 shows the characteristics of subjects at the baseline cardiovascular disease risk survey stratified by use of medication for diabetes mellitus. Among subjects not taking medication for diabetes mellitus at baseline, those with baseline HbA1c ≥8.1% were older, had higher BMI, and there was a higher proportion of current smokers, higher systolic blood pressure, higher serum LDL cholesterol, and lower HDL cholesterol, compared to subjects whose baseline HbA1c was <5.7 %. Among subjects on medication for diabetes mellitus at baseline, subjects with baseline HbA1c ≥8.1% were younger than subjects whose baseline HbA1c was <5.7 %.

Table 3 presents the multivariable-adjusted ORs and 95% CIs for retinal hemorrhage and diabetic retinal hemorrhage according to HbA1c category, stratified by use of medication for diabetes mellitus at baseline. For subjects not taking medication for diabetes mellitus at baseline, compared with the referent group whose baseline HbA1c was < 5.7%, subjects with baseline HbA1c from ≥7.3 to <8.1% and ≥8.1% were at a significantly higher risk of retinal hemorrhage (P<0.001 and P<0.001, respectively) and subjects with baseline HbA1c from ≥5.7 to <6.5%, ≥6.5 to <7.3%, ≥7.3 to <8.1%, and ≥8.1% were at a significantly higher risk of diabetic retinal hemorrhage (P<0.001, P<0.001, P<0.001 and P<0.001, respectively). Among subjects receiving glucose-lowering agents at baseline, there was no significant association between HbA1c and the risk of retinal hemorrhage or diabetic retinal hemorrhage. There was no significant association between HbA1c and the risk of

non-diabetic retinal hemorrhage among subjects who were not taking medication for diabetes mellitus at baseline.

Figure 1 shows the Kaplan–Meier plots for the five HbA1c categories and diabetic retinal hemorrhage among subjects not taking medication for diabetes mellitus at baseline. The proportion of subjects that were hemorrhage-free was 99.8% for those with HbA1c <5.7%, 96.3% for HbA1c ≥5.7 to <6.5%, 92.7% for HbA1c ≥6.5 to <7.3%, 45.9% for HbA1c ≥7.3 to <8.1%, and 38.1% for HbA1c ≥8.1% (P<0.001, log-rank test).

Table 4 shows the multivariable-adjusted ORs and 95% CIs for cardiovascular risk factors for retinal hemorrhage and diabetic retinal hemorrhage among subjects not taking medication for diabetes mellitus at baseline. Age, BMI, and hypertension were positively associated with the risk of retinal hemorrhage (P<0.001, P=0.017, and P<0.001, respectively), while the initiation of cholesterol-lowering medication was inversely associated with the risk of hemorrhage (P=0.011). Smoking was positively associated with the risk of diabetic retinal hemorrhage (P=0.028).

In addition, we examined the relationship between HbA1c and the risk of retinal hemorrhage in both eyes, and found similar results (Supplemental table 2). Compared with the referent group whose baseline HbA1c was < 5.7%, subjects with baseline HbA1c ≥8.1% not taking medication for diabetes mellitus at baseline were had a 8.30-fold higher risk of retinal hemorrhage and a 240.22-fold higher risk of diabetic retinal hemorrhage (P<0.001 and P<0.001, respectively). For subjects receiving glucose-lowering agents at baseline, there was no significant association between HbA1c and the risk of retinal hemorrhage or diabetic retinal hemorrhage. We also examined the relationship between HbA1c and the risk of retinal hemorrhage among workers. Compared with the referent group whose baseline HbA1c was < 5.7%, subjects with baseline HbA1c ≥8.1% had a 3.10-fold higher risk of retinal hemorrhage

and a 248.12-fold higher risk of diabetic retinal hemorrhage ($P<0.001$ and $P<0.001$, respectively) (Supplemental Table 3).

4. Discussion

We found a significant positive relationship between HbA1c and the risk of subsequent retinal hemorrhage among subjects not taking medication for diabetes mellitus at baseline. This relationship was observed for both retinal hemorrhage and diabetic retinal hemorrhage. This is the first study that shows an association between HbA1c and the risk of retinal hemorrhage. The study also showed that aging, BMI, and hypertension were positively correlated with the risk of retinal hemorrhage, and initiation of treatment for hypercholesterolemia was inversely correlated with the risk of retinal hemorrhage. Smoking was positively correlated with the risk of diabetic retinal hemorrhage. These associations were observed among subjects not receiving medication for diabetes mellitus at baseline, but among not subjects on medication.

Several previous studies have reported a positive relationship between HbA1c and the risk of diabetic retinopathy (3-5); however, the relationship between HbA1c(HbA1) and the risk of retinal hemorrhage was not reported. A Japanese study based on health check-ups used fundus photography to evaluate for diabetic retinopathy (5) based on Fukuda standard A2 or higher as the definition of diabetic retinopathy (9). In short, that study defined diabetic retinopathy as the presence of hard exudates, cotton wool spots, retinal hemorrhage, or more severe forms of retinopathy. Unfortunately, that study did not report the number of retinal hemorrhages or the association between HbA1c and the risk of retinal hemorrhage itself. Therefore, we could not compare our results with their results.

In the present study, several cardiovascular risk factors were positively associated with the risk of retinal hemorrhage, such as hypertension, BMI, and smoking. For hypertension, initiation of anti-hypertensive medication was also inversely associated with the risk of retinal hemorrhage and diabetic retinal hemorrhage with borderline significance. Of course, the mechanism is unknown, but these findings imply that the prevention of retinal

hemorrhage is similar to the prevention of stroke, especially intraparenchymal hemorrhage, which is due to arterial necrosis and associated with susceptibility to arterial wall rupture (10).

The methodology of the present study had certain strengths. It was a population-based prospective study, which is more representative of the general population than studies with hospital-based or volunteer samples. In addition, a prospective study has little recall bias, and the results of such studies support a potential causal relationship between risk factors and events.

The present study also had limitations. First, the protocols of fundus photography varied among subjects, which may result in detection bias. The two lowest categories of HbA1c included subjects who took retinal photography biennially. Therefore, these categories may have not identified cases of retinal hemorrhage between surveys. However, we examined the association between HbA1c and the risk of retinal hemorrhage among workers because this group underwent fundus photography annually (Supplemental table 3). We confirmed the association between HbA1c and the risk of retinal hemorrhage did not change materially. Second, we used data from a single eye, usually the right eye. Therefore, we did not capture cases of retinal hemorrhage in the left eye. However, this detection bias shifts the results toward null and does not artificially create an apparent association between HbA1c and the risk of retinal hemorrhage. We performed some analyses with data from both eyes (Supplemental Table 2) and confirmed that the estimate of the association between HbA1c and the risk of retinal hemorrhage was not materially different. Third, we could not ascertain the precise incident time of retinal hemorrhage because our analysis was based on an annual cardiovascular disease risk survey. Therefore, we used logistic regression to calculate ORs. Fourth, we used two different outcomes, retinal hemorrhage and diabetic retinal hemorrhage, which constituted 18.9% of all retinal

hemorrhages. Although we defined diabetic retinal hemorrhage using the criteria stated in the Methods section, misclassification may have occurred.

In conclusion, our prospective study of the Japanese general population demonstrated that HbA1c is positively associated with the risk of retinal hemorrhage among subjects not on glucose-lowering treatment at the time of the baseline survey. In addition, several cardiovascular risk factors such as hypertension are associated with the risk of retinal hemorrhage.

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Study Collaborators

The Circulatory Risk in Communities Study (CIRCS) is a collaborative study managed by the Osaka Center for Cancer and Cardiovascular Disease Prevention, University of Tsukuba, Osaka University, Fukushima Medical University, Dokkyo Medical University, Ehime University, and Juntendo University. The current CIRCS investigators are: Masahiko Kiyama, Takeo Okada, Isao Muraki, Mina Hayama, Takeshi Sawai, Shinichi Sato and Yuji Shimizu (Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka); Tomoko Sankai and Kazumasa Yamagishi (University of Tsukuba, Tsukuba); Hiroyasu Iso, Akihiko Kitamura, Hironori Imano, and Renzhe Cui (Osaka University, Suita); Tetsuya Ohira (Fukushima Medical University, Fukushima); Mitsumasa Umesawa and Masanori Nagao (Dokkyo Medical University, Mibu); Shinichi Hitsumoto and Isao Saito (Ehime University, Tōon); and Takeshi Tanigawa, Ai Ikeda and Kotatsu Maruyama (Juntendo University, Tokyo).

Conflicts of Interest

There are no potential conflicts of interest relevant to this manuscript.

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Table 1. Number of retinal hemorrhages stratified by use of medication for diabetes mellitus at baseline

	No medication for diabetes at baseline	Medication for diabetes at baseline	Total
No. of subjects	11429	215	11644
Person-years	53982	844	54826
Retinal hemorrhage			
No. of events	451	58	509
Diabetic retinal hemorrhage			
No. of events	41	55	96
Non-diabetic retinal hemorrhage			
No. of events	410	3	413

Table 2. Characteristics of subjects by HbA1c category at baseline

	No medication for diabetes mellitus at baseline					Medication for diabetes mellitus at baseline				
	HbA1c (%)					HbA1c (%)				
	<5.7	≥5.7 to <6.5	≥6.5 to <7.3	≥7.3 to <8.1	≥8.1	<5.7	≥5.7 to <6.5	≥6.5 to <7.3	≥7.3 to <8.1	≥8.1
No. of subjects	10428	758	136	47	60	11	45	62	50	47
Age (years)	48.3	56.2**	55.6**	55.1**	54.1**	64.9	58.8	62.1	59.2	55.8**
Male (%)	60	60	65	77*	73*	73	67	81	74	70
Body mass index (kg/m^2)	23.1	24.9**	25.6**	24.6**	25.1**	23.7	24.2	24.0	25.3	24.1
Current drinkers (%)	57	52**	50	57	58	58	55	54	60	59
Current smokers (%)	31	34	40*	37	53**	36	30	39	30	34
Systolic blood pressure (mmHg)	123	126**	129**	129**	128**	131	130	132	133	130
Diastolic blood pressure (mmHg)	77	79**	80**	79	78	78	76	78	79	77
Medication for hypertension at baseline (%)	11	14**	15	20*	5	40	40	35	34	28
Serum LDL cholesterol (mg/dL)	125	131**	134**	129	139**	99	121	128	127	128
Serum HDL cholesterol (mg/dL)	59	56**	54**	53**	53**	56	52	56	57	56
Medication for hypercholesterolemia at baseline (%)	4	9**	7	9	0	17	26	18	26	15
Initiation of glucose-lowering medication after baseline (%)	1	10**	41**	59**	58**	-	-	-	-	-
Initiation of anti-hypertensive medication after baseline (%)	7	8	13**	13	8	8	10	4	12	7
Initiation of cholesterol-lowering medication after baseline (%)	5	7	11**	12	12*	10	9	10	4	14

Abbreviations: HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Difference from the lowest category $^{*}P<0.05$ $^{**}P<0.01$

Except for age and male sex, values shown were adjusted for age and sex.

Table 3. Associations between HbA1c and risk of retinal hemorrhage in one eye

	HbA1c (%)				
	<5.7	≥5.7 to <6.5	≥6.5 to <7.3	≥7.3 to <8.1	≥8.1
No medication for diabetes at baseline					
No. of subjects	10428	758	136	47	60
Retinal hemorrhage					
No. of events	375	40	10	11	15
Incidence (/1000 person-years)	7.5	13.3	16.7	45.8	68.4
Multivariable-adjusted OR and 95%CI[a]	1.00	0.90 (0.64 - 1.28)	1.17 (0.58 - 2.37)	4.66 (2.14 - 10.16)	5.41 (2.71 - 10.81)
Diabetic retinal hemorrhage					
No. of events	7	7	6	9	12
Incidence (/1000 person years)	0.1	2.3	10.0	37.5	54.7
Multivariable-adjusted OR and 95%CI[a]	1.00	11.26 (3.74 - 33.89)	44.51 (12.77 - 155.11)	233.08 (67.68 - 802.65)	238.87 (74.36 - 767.38)
Medication for diabetes at baseline					
No. of subjects	11	45	62	50	47
Retinal hemorrhage					
No. of events	2	9	15	15	17
Incidence (/1000 person-years)	30.5	43.8	61.9	86.8	108.0
Multivariable-adjusted OR and 95%CI[a]	1.00	1.00 (0.17 - 5.70)	1.43 (0.27 - 7.72)	1.87 (0.34 - 10.33)	2.20 (0.40 - 12.23)
Diabetic retinal hemorrhage					
No. of events	2	9	14	15	15
Incidence (/1000 person-years)	30.5	43.8	57.8	86.8	95.3
Multivariable-adjusted OR and 95%CI[a]	1.00	0.99 (0.17 - 5.65)	1.25 (0.23 - 6.77)	1.83 (0.33 - 10.15)	1.80 (0.32 - 10.05)

Abbreviations: CI, confidence interval; OR, odds ratio; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein..

[a]Adjusted for age, sex, body mass index, current drinker, current smoker, hypertension, serum LDL cholesterol (10 mg/dL), serum HDL cholesterol (10 mg/dL), initiation of glucose-lowering medication, initiation of antihypertensive medication, and initiation of cholesterol-lowering medication.

Table 4. Multivariable-adjusted odds ratios for cardiovascular risk factors for retinal hemorrhage in a single eye among subjects not taking medication for diabetes mellitus at baseline

	Retinal hemorrhage					P	Diabetic retinal hemorrhage					P
No. of subjects			11429						11429			
No. of events			451						41			
Age (years)[a]	1.04	(	1.03	-	1.05	)	<0.001	1.02	(	0.99	-	1.06	)	0.250
Sex (female)[a]	1.14	(	0.89	-	1.47	)	0.306	0.76	(	0.30	-	1.96	)	0.572
BMI (kg/m^2)[a]	1.03	(	1.00	-	1.06	)	0.017	0.97	(	0.88	-	1.07	)	0.559
Current smoker[a]	1.24	(	0.98	-	1.56	)	0.077	2.44	(	1.10	-	5.41	)	0.028
Current drinker[a]	0.82	(	0.65	-	1.04	)	0.099	0.56	(	0.24	-	1.30	)	0.176
Hypertension[a]	2.19	(	1.76	-	2.73	)	<0.001	1.72	(	0.83	-	3.57	)	0.147
Serum LDL cholesterol (10 mg/dL)[a]	1.01	(	0.97	-	1.04	)	0.759	0.95	(	0.86	-	1.05	)	0.311
Serum HDL cholesterol (10 mg/dL)[a]	0.98	(	0.91	-	1.05	)	0.537	1.16	(	0.90	-	1.50	)	0.258
Initiation of glucose-lowering medication after baseline examination[a]	1.44	(	0.85	-	2.44	)	0.174	2.11	(	0.90	-	4.93	)	0.087
Initiation of anti-hypertensive medication after baseline examination[a]	0.74	(	0.52	-	1.06	)	0.096	0.22	(	0.05	-	1.03	)	0.054
Initiation of cholesterol-lowering medication after baseline examination[a]	0.56	(	0.35	-	0.87	)	0.011	1.31	(	0.43	-	4.01	)	0.633

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein..

[a]Adjusted for HbA1c categories and the other variables.

Supplementary Table 1. Characteristics of subjects stratified by background at baseline

	Residents	Workers
No. of subjects	4834	6810
Age (years)	56.3	44.0**
Male (%)	38	76**
Body mass index (kg/m^2)	23.5	23.1**
Current drinkers (%)	51	61**
Current smokers (%)	32	31
Systolic blood pressure (mmHg)	125	122**
Diastolic blood pressure (mmHg)	79	76**
Medication for hypertension at baseline (%)	12	11
Serum LDL cholesterol (mg/dL)	125	126*
Serum HDL cholesterol (mg/dL)	60	58**
Medication for hypercholesterolemia at baseline (%)	4	5**
Initiation of glucose-lowering medication after baseline (%)	2	2
Initiation of anti-hypertensive medication after baseline (%)	9	6**
Initiation of cholesterol-lowering medication after baseline (%)	7	5**
HbA1c (%)	5.2	5.2
Medication for diabetes mellitus at baseline (%)	2	2

Difference between affiliations $^{*}P<0.05$ $^{**}P<0.01$

Except for age and male sex, values shown were adjusted for age and sex.

Supplementary Table 2. Associations between HbA1c and risk of retinal hemorrhage in both eyes

	HbA1c (%)				
	<5.7	≥5.7 to <6.5	≥6.5 to <7.3	≥7.3 to <8.1	≥8.1
No medication for diabetes at baseline					
No. of subjects	10414	757	136	47	60
Retinal hemorrhage					
No. of events	400	52	17	12	20
Incidence (/1000 person-years)	8.0	17.4	28.9	52.0	95.5
Multivariable-adjusted OR and 95%CI[a]	1.00	1.11 (0.81 - 1.52)	2.04 (1.15 - 3.62)	5.16 (2.46 - 10.85)	8.30 (4.41 - 15.62)
Diabetic retinal hemorrhage					
No. of events	11	13	8	8	17
Incidence (/1000 person years)	0.2	4.4	13.6	34.7	81.2
Multivariable-adjusted OR and 95%CI[a]	1.00	11.99 (5.14 - 27.98)	35.93 (12.70 - 101.68)	121.10 (40.29 - 363.95)	240.22 (91.46 - 630.89)
Medication for diabetes at baseline					
No. of subjects	11	45	62	50	47
Retinal hemorrhage					
No. of events	2	11	19	18	20
Incidence of events (/1000 person years)	30.5	55.4	87.4	112.7	145.7
Multivariable-adjusted OR and 95%CI[a]	1.00	1.18 (0.21 - 6.65)	2.15 (0.40 - 11.57)	2.31 (0.42 - 12.72)	2.83 (0.51 - 15.69)
Diabetic retinal hemorrhage					
No. of events	2	10	16	17	18
Incidence (/1000 person-years)	30.5	50.4	73.6	106.4	131.1
Multivariable-adjusted OR and 95%CI[a]	1.00	1.05 (0.19 - 5.96)	1.55 (0.29 - 8.37)	2.07 (0.38 - 11.35)	2.33 (0.42 - 12.85)

Abbreviations: CI, confidence interval; OR, odds ratio; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein..

[a]Adjusted for age, sex, body mass index (kg/m^2), current drinker, current smoker, hypertension, serum LDL cholesterol levels (10 mg/dL), serum HDL cholesterol levels (10 mg/dL), start of glucose-lowering medication use, start of antihypertensive medication use and start of cholesterol-lowering medication use.

Supplementary Table 3. Associations between HbA1c level and risk of retinal hemorrhage in single eyes among workers

	HbA1c (%)				
	<5.7	≥5.7 to <6.5	≥6.5 to <7.3	≥7.3 to <8.1	≥8.1
No medication for diabetes at baseline					
No. of subjects	6264	329	64	24	32
Retinal hemorrhage					
No. of events	177	7	3	7	5
Incidence (/1000 person-years)	6.5	6.8	10.5	53.5	44.3
Multivariable-adjusted OR and 95%CI[a]	1.00	0.43 (0.20 - 0.94)	0.73 (0.21 - 2.62)	8.36 (2.98 - 23.47)	3.10 (1.01 - 9.54)
Diabetic retinal hemorrhage					
No. of events	3	2	1	7	5
Incidence (/1000 person-years)	0.1	2.0	3.5	53.5	44.3
Multivariable-adjusted OR and 95%CI[a]	1.00	11.04 (1.57 - 77.88)	22.87 (1.57 - 332.62)	845.33 (134.97 - >999.99)	248.12 (39.03 - >999.99)
Medication for diabetes at baseline					
No. of subjects	0	20	27	27	23
Retinal hemorrhage					
No. of events	0	3	1	12	7
Incidence (/1000 person-years)	-	35.8	11.7	162.3	128.7
Multivariable-adjusted OR and 95%CI[a]	-	-	-	-	-
Diabetic retinal hemorrhage					
No. of events	0	3	0	12	6
Incidence (/1000 person-years)	-	35.8	0.0	162.3	110.3
Multivariable-adjusted OR and 95%CI[a]	-	-	-	-	-

Abbreviations: CI, confidence interval; OR, odds ratio; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein..

[a]Adjusted for age, sex, body mass index (kg/m^2), current drinker, current smoker, hypertension, serum LDL cholesterol (10 mg/dL), serum HDL cholesterol (10 mg/dL), initiation of glucose-lowering medication, initiation of antihypertensive medication, and initiation of cholesterol-lowering medication.

Figure 1 Kaplan–Meier plot for five HbA1c categories associated with diabetic retinal hemorrhage among subjects not receiving medication for diabetes mellitus at baseline