

Sex Differences In The Association Between Hemoglobin A1c And Cerebral White Matter Lesions In The General Japanese Population

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Abstract

The influence of diabetes and associated sex differences on cerebral white matter lesions (WMLs) is unclear. We used data from a cross-sectional study uploaded to the DATADRYAD website by Shinkawa et al. to investigate differences in the association between hemoglobin A1c (HbA1c) levels and cerebral WMLs between men and women. The average age of all participants was 56.4 ± 11.5 years old, and approximately 51.89 % of them were men. A linear relationship between HbA1c and cerebral WMLs was detected in men. Fully adjusted binary logistic regression showed no association of HbA1c with cerebral WMLs in men. A nonlinear relationship between HbA1c and cerebral WMLs was detected in women, whose cutoff point was 5.6%. The effect sizes and confidence intervals of the left and right sides of the inflection point were $OR=0.21$ (95%CI 0.06, 0.69, $P=0.0098$) and $OR=3.5$ (95%CI 1.50, 8.15, $P=0.0037$), respectively. In the higher HbA1c group, further subgroup analysis showed a stronger association between HbA1c and cerebral WMLs in women ($OR=3.83$, 95%CI 1.68, 8.72 $P=0.0014$) than in men ($OR=1.02$, 95%CI 0.76, 1.36 $P=0.8986$) (P for interaction with sex was 0.0004). A stronger effect of HbA1c on the risk of cerebral WMLs in women than in men was found in the higher HbA1c group.

Introduction

Rapid population aging combined with sedentary habits has made type 2 diabetes one of the largest public health problems worldwide^{1,2}. Recent studies have demonstrated that in addition to diabetes, prediabetes can damage small and large blood vessels and lead to complications such as neuropathy, nephropathy and macrovascular diseases³⁻⁶. More recent investigations have shown considerable sex differences associated with diabetes risk factors, hormonal effects on glucose, and diabetic vascular and nonvascular outcomes⁷⁻⁹. It has now been well established by a variety of studies that a higher HbA1c level, as a biomarker of long-term glycemic control, is an independent risk factor for diabetes complications¹⁰⁻¹². Cerebral WMLs are mainly chronic ischemic lesions caused by small vessel diseases, which show white matter hyperintensities (WMHs) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images in magnetic resonance imaging (MRI) and are associated with cognitive impairment, gait dysfunction and focal neurological signs¹³. Many factors have been found to be related to cerebral WMLs, such as age, hypertension, dyslipidemia, smoking and various biomarkers of vascular disease¹⁴. Although DM is well known as a vascular risk factor, the relationship between DM and cerebral WMLs is still controversial¹⁵⁻¹⁸. Prediabetes was also shown to be associated with brain structural abnormalities¹⁹. HbA1c, which reflects a measure of glycemia during the previous 2-3 months, is a biomarker for long-term glycemic control and is also indicative of prediabetes. Previous studies have shown a significant association between HbA1c and cerebral WMLs²⁰⁻²². However, such conclusions were not confirmed by another study conducted in a larger cohort of patients²³. In addition, the sex differences in the relationship between HbA1c and cerebral WMLs have still not been illuminated in previous studies.

In this study, a secondary data analysis was performed using existing data from a published paper²⁴. In the secondary analysis, the independent variable and dependent variable were HbA1c level and cerebral WMLs, respectively. Other covariates are consistent with those in the original. This analysis sought to investigate whether sex differences exist in the association between HbA1c levels and the incident risk of cerebral WMLs in the general population.

Results

Baseline characteristics of participants

A total of 1904 participants were included in the final data analysis, with 988 men and 916 women classified into two groups (lower HbA1c group and higher HbA1c group) according to the clinical cutoff point of HbA1c. The baseline characteristics of these groups are reported in Table 1. In general, the average age of the 1904 participants was 56.4 ± 11.5 years old, and approximately 51.89% of them were male. No statistically significant differences were detected in LDL, HbA1c, or medication to reduce blood sugar or insulin injection between men and women in the lower HbA1c group (all p values > 0.05). Women had higher values in age and HDL and were more likely to exhibit the following values than men in the lower HbA1c group: metabolic syndrome (no), smoking habit (no), medication to reduce blood pressure (no), medication to reduce the level of cholesterol (yes), amount of drinking per day (< 180 ml), drinking habit (rarely), plaque number (0) and cerebral WMLs (yes). The opposite patterns were observed in LH, TG, BS, SBP, DBP, BMI, PS, metabolic syndrome (reserve and yes), smoking habit (yes), medication to reduce blood pressure (yes), medication to reduce the level of cholesterol (no), amount of drinking per day (> 180 ml), plaque number ($n \geq 1$) and cerebral WMLs (no) in the lower HbA1c group. No statistically significant differences were detected in SBP or medication to reduce the level of cholesterol between men and women in the higher HbA1c group. Women had higher values of age, LDL, and HDL and were more likely to have metabolic syndrome (no), smoking habit (no), medication to reduce blood pressure (no), medication to reduce blood sugar or insulin injection (no), amount of drinking per day (< 180 ml) and drinking habit (rarely) and plaque number (0) and cerebral WMLs (yes) in the higher HbA1c group. The opposite patterns were observed in LH, TG, HbA1c, BS, DBP, BMI, PS, metabolic syndrome (reserve and yes), smoking habit (yes), medication to reduce blood pressure (yes), medication to reduce blood sugar or insulin injection (yes), amount of drinking per day (> 180 ml), drinking habit (sometimes and everyday), plaque number ($n \geq 1$) and cerebral WMLs (no).

Table 1
Baseline characteristics and level of cerebral white matter lesion risk factors by sex in the general Japanese population.

408)	HbA1c < 5.7 (%)			HbA1c ≥ 5.7 (%)		
	Men(n = 527) P value	Women(n =		Men(n = 461) P value	Women(n = 508)	
Age (years)	50.86 ± 11.78	53.45 ± 11.38	0.002	59.03 ± 10.28	61.86 ± 8.72	< 0.001
LDL (mg/dl)	115.95 ± 30.70	119.29 ± 28.56	0.098	121.23 ± 30.87	126.90 ± 30.25	0.007
HDL (mg/dl)	57.31 ± 14.43	69.38 ± 15.41	< 0.001	53.96 ± 12.90	64.95 ± 14.17	< 0.001
LH	2.16 ± 0.80	1.81 ± 0.60	< 0.001	2.37 ± 0.82	2.05 ± 0.68	< 0.001
TG (mg/dl)	125.50 ± 145.38	80.14 ± 45.66	< 0.001	139.41 ± 97.24	98.04 ± 57.60	< 0.001
HbA1c (%)	5.40 ± 0.19	5.40 ± 0.18	0.944	6.24 ± 0.86	6.01 ± 0.48	0.002
BS (mg/dl)	99.60 ± 8.01	94.95 ± 6.87	< 0.001	116.80 ± 27.06	104.53 ± 15.56	< 0.001
SBP (mmHg)	123.32 ± 15.84	118.65 ± 19.10	< 0.001	127.50 ± 18.15	125.36 ± 19.70	0.058
DBP (mmHg)	76.05 ± 11.38	70.38 ± 12.82	< 0.001	76.07 ± 11.83	72.40 ± 11.94	< 0.001
BMI	23.40 ± 2.85	21.52 ± 2.90	< 0.001	24.82 ± 3.51	22.68 ± 3.44	< 0.001
PS	1.01 ± 1.94	0.50 ± 1.24	< 0.001	1.87 ± 2.49	0.92 ± 1.74	< 0.001
Met-syn			< 0.001			< 0.001
no	387 (73.43%)	387 (94.85%)		220 (47.72%)	435 (85.63%)	
reserve	85 (16.13%)	11 (2.70%)		67 (14.53%)	33 (6.50%)	
yes	55 (10.44%)	10 (2.45%)		174 (37.74%)	40 (7.87%)	

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LH, quotient of LDL and HDL; TG, triglyceride; BS, blood glucose level; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; PS, carotid plaque score; Met-syn, metabolic syndrome; Med-bp, medication to reduce blood pressure; Med-sugar, medication to reduce blood sugar or insulin injection; Med-cho, medication to reduce the level of cholesterol; Drink-V, amount of drinking per day; WMLs, white matter lesions.

HbA1c < 5.7 (%)		HbA1c ≥ 5.7 (%)		
Smoking			< 0.001	< 0.001
no	365 (69.26%)	381 (93.38%)	330 (71.58%)	492 (96.85%)
yes	162 (30.74%)	27 (6.62%)	131 (28.42%)	16 (3.15%)
Med-bp			0.002	0.001
no	417 (79.13%)	354 (86.76%)	296 (64.21%)	375 (73.82%)
yes	110 (20.87%)	54 (13.24%)	165 (35.79%)	133 (26.18%)
Med-sugar			0.213	< 0.001
no	525 (99.62%)	408 (100.00%)	359 (77.87%)	473 (93.11%)
yes	2 (0.38%)	0 (0.00%)	102 (22.13%)	35 (6.89%)
Med-cho			0.013	0.990
no	497 (94.31%)	367 (89.95%)	345 (74.84%)	380 (74.80%)
yes	30 (5.69%)	41 (10.05%)	116 (25.16%)	128 (25.20%)
Drink-V			< 0.001	< 0.001
1	204 (38.71%)	345 (84.56%)	224 (48.59%)	451 (88.78%)
2	197 (37.38%)	50 (12.25%)	171 (37.09%)	49 (9.65%)
3	126 (23.91%)	13 (3.19%)	66 (14.32%)	8 (1.57%)
Drinking			< 0.001	< 0.001

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LH, quotient of LDL and HDL; TG, triglyceride; BS, blood glucose level; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; PS, carotid plaque score; Met-syn, metabolic syndrome; Med-bp, medication to reduce blood pressure; Med-sugar, medication to reduce blood sugar or insulin injection; Med-cho, medication to reduce the level of cholesterol; Drink-V, amount of drinking per day; WMLs, white matter lesions.

HbA1c < 5.7 (%)		HbA1c ≥ 5.7 (%)		
rarely	107 (20.30%)	223 (54.66%)	124 (26.90%)	342 (67.32%)
sometimes	172 (32.64%)	114 (27.94%)	147 (31.89%)	132 (25.98%)
everyday	248 (47.06%)	71 (17.40%)	190 (41.21%)	34 (6.69%)
n-plaque		< 0.001		< 0.001
0	359 (68.12%)	327 (80.15%)	216 (46.85%)	339 (66.73%)
1	87 (16.51%)	49 (12.01%)	105 (22.78%)	96 (18.90%)
2	48 (9.11%)	23 (5.64%)	84 (18.22%)	48 (9.45%)
3	33 (6.26%)	9 (2.21%)	56 (12.15%)	25 (4.92%)
WMLs		0.005		0.004
no	311 (59.01%)	203 (49.75%)	186 (40.35%)	160 (31.50%)
yes	216 (40.99%)	205 (50.25%)	275 (59.65%)	348 (68.50%)
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LH, quotient of LDL and HDL; TG, triglyceride; BS, blood glucose level; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; PS, carotid plaque score; Met-syn, metabolic syndrome; Med-bp, medication to reduce blood pressure; Med-sugar, medication to reduce blood sugar or insulin injection; Med-cho, medication to reduce the level of cholesterol; Drink-V, amount of drinking per day; WMLs, white matter lesions.				

Univariate analysis

We listed the results of univariate analyses, adjusting for age, for men and women in Table 2. By univariate binary logistic regression adjusting for age, we found that LDL, HDL, LH, TG, HbA1c, BS, smoking habits, amount of drinking per day and plaque number (n = 1, n = 2, n > 2) were not associated with cerebral WMLs in men. We also found that PS odds ratio (OR) = 1.09 (95%CI 1.01, 1.18 P = 0.0365), SBP OR = 1.01 (95%CI 1.00, 1.02 P = 0.0392), DBP OR = 1.02 (95%CI 1.01, 1.03 P = 0.0013), BMI OR = 1.05 (95%CI 1.00, 1.10 P = 0.0358), metabolic syndrome (reserve) OR = 1.53 (95%CI 1.00, 2.32 P = 0.0475), metabolic syndrome (yes) OR = 1.59 (95%CI 1.11, 2.28 P = 0.0113), medication to reduce blood pressure (yes) OR = 1.74 (95%CI 1.23, 2.45 P = 0.0017), medication to reduce sugar or insulin injection (yes) OR = 1.70 (95%CI 1.02, 2.85 P = 0.0425), medication to reduce the level of cholesterol (yes) OR = 1.61 (95%CI 1.06, 2.45 P = 0.0271), drinking habit (sometimes) OR = 1.79 (95%CI 1.19, 2.71 P = 0.0054), and drinking habit (every day) OR = 1.51 (95%CI 1.03, 2.22 P = 0.0355) were positively correlated with cerebral WMLs in

men. By univariate binary logistic regression adjusting for age, we found that LDL, LH, TG, HbA1c, BS, BMI, metabolic syndrome (reserve or yes), smoking habit, medication to reduce sugar or insulin injection, medication to reduce the level of cholesterol, drinking habit, plaque number (n = 1, n = 2, n > 2) and amount of drinking per day (180–360 ml) were not associated with cerebral WMLs in women. We also found that the amount of drinking per day (> 360 ml) OR = 0.14 (95%CI 0.04, 0.51 P = 0.0030) was negatively associated with cerebral WMLs in women. In contrast, univariate analysis showed that PS OR = 1.20 (95%CI 1.05, 1.38 P = 0.0093), HDL OR = 1.01 (95%CI 1.00, 1.02 P = 0.0491), SBP OR = 1.01 (95%CI 1.00, 1.02 P = 0.0136), DBP OR = 1.02 (95%CI 1.01, 1.03 P = 0.0007), medication to reduce blood pressure (yes) OR = 1.91 (95%CI 1.23, 2.98 P = 0.0041), and plaque number (n > 2) OR = 8.86 (95%CI 1.18, 66.42 P = 0.0338) were positively associated with cerebral WMLs in women.

Table 2 The results of the univariate analysis, adjusting for age, relationship between HbA1c and cerebral WMLs

Crude association of cerebral WMLs with risk factors and characteristics adjusting for age.

	Men	Women	Total
PS	1.09 (1.01, 1.18) 0.0365	1.20 (1.05, 1.38) 0.0093	1.12 (1.05, 1.20) 0.0010
LDL (mg/dl)	1.00 (1.00, 1.01) 0.5653	1.00 (1.00, 1.01) 0.6444	1.00 (1.00, 1.00) 0.5939
HDL (mg/dl)	1.01 (0.99, 1.02) 0.3316	1.01 (1.00, 1.02) 0.0491	1.01 (1.00, 1.02) 0.0291
LH	1.00 (0.83, 1.21) 0.9790	0.95 (0.76, 1.20) 0.6824	0.97 (0.84, 1.12) 0.6633
TG (mg/dl)	1.00 (1.00, 1.00) 0.6516	1.00 (1.00, 1.00) 0.5256	1.00 (1.00, 1.00) 0.9972
HbA1c (%)	1.10 (0.91, 1.34) 0.3133	1.32 (0.90, 1.93) 0.1576	1.14 (0.96, 1.35) 0.1306
BS (mg/dl)	1.00 (1.00, 1.01) 0.1744	1.00 (0.99, 1.01) 0.7592	1.00 (1.00, 1.01) 0.1902
SBP (mmHg)	1.01 (1.00, 1.02) 0.0392	1.01 (1.00, 1.02) 0.0136	1.01 (1.00, 1.02) 0.0018
DBP (mmHg)	1.02 (1.01, 1.03) 0.0013	1.02 (1.01, 1.03) 0.0007	1.02 (1.01, 1.03) <0.0001
BMI	1.05 (1.00, 1.10) 0.0358	1.01 (0.96, 1.06) 0.6710	1.03 (1.00, 1.06) 0.0904
Met-syn			
no	1.0	1.0	1.0
reserve	1.53 (1.00, 2.32) 0.0475	2.30 (1.00, 5.32) 0.0505	1.64 (1.14, 2.36) 0.0082
yes	1.59 (1.11, 2.28) 0.0113	1.44 (0.69, 3.02) 0.3282	1.59 (1.15, 2.19) 0.0047
Smoking			
no	1.0	1.0	1.0
yes	0.97 (0.70, 1.35) 0.8711	0.61 (0.30, 1.22) 0.1616	0.89 (0.66, 1.18) 0.4132
Med-bp			
no	1.0	1.0	1.0
yes	1.74 (1.23, 2.45) 0.0017	1.91 (1.23, 2.98) 0.0041	1.81 (1.38, 2.37) <0.0001
Med-sugar			
no	1.0	1.0	1.0
yes	1.70 (1.02, 2.85) 0.0425	1.77 (0.66, 4.75) 0.2566	1.73 (1.10, 2.73) 0.0171
Med-cho			
no	1.0	1.0	1.0
yes	1.61 (1.06, 2.45) 0.0271	1.29 (0.84, 1.99) 0.2511	1.42 (1.05, 1.92) 0.0228
Drink-V			
1	1.0	1.0	1.0

2	1.11 (0.80, 1.55) 0.5356	0.91 (0.57, 1.45) 0.6813	1.00 (0.77, 1.31) 0.9942
3	1.32 (0.88, 1.98) 0.1743	0.14 (0.04, 0.51) 0.0030	0.99 (0.69, 1.42) 0.9511
Drinking habit			
rarely	1.0	1.0	1.0
sometimes	1.79 (1.19, 2.71) 0.0054	0.97 (0.69, 1.38) 0.8836	1.24 (0.95, 1.62) 0.1111
every day	1.51 (1.03, 2.22) 0.0355	0.71 (0.44, 1.14) 0.1572	1.07 (0.81, 1.43) 0.6154
n-plaque			
0	1.0	1.0	1.0
1	1.45 (0.99, 2.12) 0.0595	0.88 (0.58, 1.34) 0.5501	1.17 (0.88, 1.56) 0.2777
2	1.46 (0.91, 2.32) 0.1140	1.54 (0.82, 2.91) 0.1818	1.48 (1.02, 2.15) 0.0375
3	1.79 (0.99, 3.25) 0.0539	8.86 (1.18, 66.42) 0.0338	2.21 (1.29, 3.78) 0.0038

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LH, quotient of LDL and HDL; TG, triglyceride; BS, blood glucose level; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; PS, carotid plaque score; Met-syn, metabolic syndrome; Med-bp, medication to reduce blood pressure; Med-sugar, medication to reduce blood sugar or insulin injection; Med-cho, medication to reduce the level of cholesterol; Drink-V, amount of drinking per day.

Results of unadjusted and adjusted binary logistic regression

The results of nonlinearity of HbA1c and cerebral white matter lesions for men and women

In the present study, we analyzed the nonlinear relationship between HbA1c and cerebral WMLs for men and women (Fig. 1a and Fig. 1b). The smooth curve and the result of the generalized additive model showed a linear association of HbA1c with cerebral WMLs in men after adjusting for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habit and plaque number. In this study, we constructed two models to analyze the independent effects of HbA1c on cerebral WMLs (univariate and multivariate binary logistic regression). Binary logistic regression showed that there was no association of HbA1c with cerebral WMLs in men. The effect sizes (OR) and 95% confidence intervals are listed in Table 3. In the minimally adjusted model (model 1), the model-based effect size can be explained as a one-unit difference in HbA1c level associated with risk of WMLs. The smooth curve and the result of the generalized additive model showed that the relationship between HbA1c and cerebral WMLs was nonlinear in women after adjusting for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habit and plaque number. We used both binary logistic regression and two-piecewise binary logistic regression to fit the association and select the best fit model based on P for the log likelihood ratio test.

Table 3

Multiple regression analysis of the relationship between HbA1c and cerebral WMLs in men

Variable	Minimally adjusted model (OR, 95%CI, P)	Fully adjusted model (OR, 95%CI, P)
HbA1c (%)	1.10 (0.91, 1.34) 0.3133	0.87 (0.59, 1.29) 0.4998
Minimally adjusted model: we adjusted for age.		
Fully adjusted model: we adjusted for age, HDL, LDL, TG, DBP, SBP, BMI, BS, PS, drinking habit, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce cholesterol levels, and n-plaque.		

Because the P for the log likelihood ratio test was less than 0.05, we chose two-piecewise binary logistic regression for fitting the association between HbA1c and cerebral WMLs in women because it can accurately represent the relationship. Using a two-piecewise binary logistic regression and recursive algorithm, we calculated that the inflection point was 5.6%. On the left side of the inflection point, the effect size and 95%CI were 0.21 (0.06, 0.69), $P = 0.0098$. On the right side of the inflection point, the effect size and 95%CI were 3.5 (1.50, 8.15) ($P = 0.0037$) (Table 4).

Table 4 The results of the two-piecewise linear regression model in women

For exposure: HbA1c

For outcome: WMLs

Model I	
one linear regression coefficient	1.41 (0.83, 2.37) 0.2018
Model II	
Inflection point(K)	5.6
< K-segment regression coefficient 1	0.21 (0.06, 0.69) 0.0098
> K-segment regression coefficient 2	3.5 (1.50, 8.15) 0.0037
The difference between regression coefficient 2 and 1	16.77 (3.35, 84.01) 0.0006
Predicted value of Y at the inflection point	0.23 (0.01, 0.44)
Log Likelihood Ratio Tests	<0.001

Effect: cerebral WMLs, Cause: HbA1c

We adjusted for age, HDL, LDL, TGs, DBP, SBP, BMI, BS, PS, drinking habits, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, and medication to reduce cholesterol and n-plaque levels.

Interaction test

We used sex as the stratification variable to observe the trend of effect sizes in this variable (Table 5). We noted that there was an interaction between sex and HbA1c based on our a priori specification in the higher HbA1c group (HbA1c \geq 5.7 mmol/L) (P values for interaction $<$ 0.05). In this study, a stronger association was detected in women (OR = 3.83 95%CI 1.68, 8.72, P = 0.0014) than in men (OR = 1.02 95%CI 0.76, 1.36, P = 0.8986) in the higher HbA1c group.

Table 5

Effect size of HbA1c on cerebral white matter lesions in subgroups stratified by sex and HbA1c

Model	Men	Women	P interaction
HbA1c < 5.7%			
Crude	1.77 (0.68, 4.56) 0.2392	2.46 (0.80, 7.56) 0.1171	0.6606
Model I	1.24 (0.40, 3.84) 0.7126	0.18 (0.05, 0.67) 0.0109	0.0283
Model I*	1.23 (0.38, 3.94) 0.7295	0.25 (0.06, 0.97) 0.0448	0.0799
Model II	1.36 (0.45, 4.05) 0.5853	1.13 (0.33, 3.85) 0.8479	0.8228
Model II*	1.69 (0.56, 5.13) 0.3515	0.85 (0.24, 3.05) 0.8086	0.4259
HbA1c ≥ 5.7%			
Crude	1.10 (0.88, 1.38) 0.4021	4.22 (2.01, 8.87) 0.0001	0.0001
Model I	1.12 (0.89, 1.41) 0.3255	2.34 (1.16, 4.72) 0.0173	0.0304
Model I*	1.12 (0.89, 1.41) 0.3281	2.32 (1.14, 4.69) 0.0196	0.0338
Model II	0.98 (0.74, 1.31) 0.9038	3.96 (1.78, 8.82) 0.0007	< 0.0001
Model II*	1.02 (0.76, 1.36) 0.8986	3.83 (1.68, 8.72) 0.0014	0.0004
Total			
Crude	1.24 (1.00, 1.54) 0.0496	2.42 (1.55, 3.80) 0.0001	0.0018
Model I	1.17 (0.94, 1.44) 0.1514	1.33 (0.87, 2.03) 0.1850	0.5459
Model I*	1.16 (0.93, 1.43) 0.1809	1.46 (0.93, 2.30) 0.0976	0.3014
Model II	1.00 (0.76, 1.30) 0.9877	2.15 (1.32, 3.51) 0.0021	0.0006
Model II*	1.04 (0.80, 1.36) 0.7621	1.94 (1.18, 3.16) 0.0085	0.0085
Model I: Adjusted for age			
Model I*: Adjusted for age and the interaction terms for age			
Model II: Adjusted for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habits, and plaque number			
Model II*: Adjusted for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habits, plaque number and the interaction terms for following variables: age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habits, plaque number			

Discussion

In this population-based retrospective cohort study, we found that there was no association of HbA1c with cerebral WMLs in men. Our findings indicate a nonlinear relationship between HbA1c and cerebral WMLs in women after adjusting for other covariates, for whom the cutoff point was 5.6%. This result suggests a U shape of the independent association between HbA1c and cerebral WMLs in women. In addition, we also found that the trend of the effect sizes on the left and right sides of the inflection point was not consistent (left OR = 0.21 95%CI 0.06, 0.69 P = 0.0098); right OR = 3.5 95%CI 1.50, 8.15 P = 0.0037). Interaction tests will help us to better understand the trends of HbA1c and cerebral WMLs in different populations. The results of this study found a stronger association between HbA1c levels and cerebral WMLs in women than in men in the higher HbA1c group.

Individuals with diabetes are at high risk of various complications, mostly vascular-associated complications, such as cardiovascular disease, stroke, neuropathy, nephropathy and retinopathy. However, the risks of complications in individuals with diabetes are different. More recent data have clearly demonstrated that the pathophysiology and excess risk of vascular and nonvascular outcomes of diabetes vary by sex^{7,9}. Data suggest that cardiovascular risk factors present a higher burden and greater effect on women with diabetes than on men with diabetes^{8,25-27}. However, sex differences in the association between diabetes and cerebral WMLs have not yet been illuminated. Over the last few years, many studies concentrating on the possible determinants of cerebral WMLs have suggested chronic ischemic pathogenesis in the development and progression of WMD. Among the many vascular risk factors possibly implicated in the pathogenesis of cerebral WMLs, type 2 diabetes mellitus has been a strong risk factor. Studies have shown that structural brain abnormalities already occur in prediabetes as well as diabetes¹⁹. Nearly half of previous studies reported a statistically significant association between diabetes mellitus and cerebral WMLs, while the others reported the opposite¹⁵. A study by Saczynski et al. showed that participants with type 2 diabetes had a higher percentage of WMLs after adjustment for demographic and cardiovascular risk factors in a sample of 4415 participants²⁸. Van Agtmaal et al. suggested that prediabetes and type 2 diabetes were associated with larger white matter hyperintensities¹⁹. Similar findings were also reported in studies by Espeland M.A. and Ropele S^{29,30}. However, there are some other studies that are inconsistent with those above. R. Nick Bryan et al. reported that there was no association of diabetes characteristics with small vessel ischemic disease in the brain in their sample of patients with type 2 diabetes mellitus³¹. A study by Moran et al. showed that type 2 diabetes mellitus was not associated with microbleeds or WMHs¹⁶. A large-scale systematic review considered imaging methods with different sensitivities used to study the extent of WMLs, which may contribute to the inconsistency in conclusions on the association between DM and WMLs¹⁵. We analyzed the reasons why these studies are inconsistent, and we speculate that the reasons for the different results may be due to the following factors: (1) the research populations are different; (2) the different conclusions do not clarify the nonlinear relationship; (3) the different conclusions do not clarify sex differences in the relationship between HbA1c and cerebral WMLs; and (4) the studies did not take into account the effect of plaque number and carotid plaque score on the HbA1c and cerebral WML

relationship when adjusting for covariates. However, previous studies have confirmed that these variables are related to HbA1c or cerebral WMLs³².

Our study showed that a higher level of HbA1c has a greater impact on women's risk for WMLs than on men's risk. The inflection point of the U shape on the independent association between HbA1c and cerebral WMLs was 5.6%. This indicated that more aggressive treatment should be considered in women for cerebral WML prevention and for glycemic targets in Japan. When HbA1c is lower than 5.6%, the level of HbA1c is negatively associated with cerebral WMLs, which indicates that hypoglycemic conditions may also contribute to the development of cerebral WMLs. The mechanisms that explain the sex difference in the risk of vascular disease associated with diabetes have not been identified. However, this excess risk among women could be due to certain underlying biological differences and health care provided for diabetes and its vascular complications between women and men³³. Several studies supported that women underwent more pronounced exposure to hazardous metabolic risk factors than men before the onset of type 2 diabetes³⁴⁻³⁷. Among 500,000 individuals in the UK Biobank, the difference in waist circumference and BMI between those with and without diabetes was larger in women than men³⁸. Moreover, women have similar levels of HbA1c but a remarkably higher BMI than men when first diagnosed with diabetes^{39,40}. These disadvantageous obesity-associated mechanisms in women were speculated to be partly responsible for the sex difference in the risk of vascular disease associated with diabetes. In contrast to the above conclusions, our study showed a lower BMI in women than in men in the higher HbA1c group. Previous studies showed that women who converted to diabetes showed relatively worse levels of total cholesterol, HDL cholesterol, triglycerides and DBP at baseline than men. In contrast, women with higher levels of HbA1c had relatively better levels of LH, TG and DBP than men in the Japanese population. In addition to biological differences between men and women, disparities in health care may in part explain sex differences in diabetes-related vascular complications. Previous studies showed that secondary prevention in risk factor management was generally worse in women than in men⁴¹. Our study showed a similar outcome. Women with higher levels of HbA1c are less likely to take medicine for BP and blood sugar than men. Sex differences in biological factors, such as both the use and provision of health care, could contribute to women's higher relative risk of diabetic vascular complications. There were still significant sex differences in the association between HbA1c and cerebral WMLs after adjusting for associated covariates.

The clinical value of this study is as follows: (1) To the best of our knowledge, this is the first study to observe the independent nonlinear association between HbA1c and cerebral WMLs in women; (2) to the best of our knowledge, this is the first study to observe sex differences in the association between HbA1c and cerebral WMLs in women and men; and (3) the findings from this study should contribute to future research on the establishment of diagnostic or predictive models of cerebral WMLs.

Our study has some strengths. (1) We performed a large population-based analysis of the general population; (2) we address the nonlinearity in the present study and further explore this; (3) as this is an observational study, it was susceptible to various confounding variables. We used strict statistical

adjustments to minimize residual confounding; and (4) the effect modifier factor analysis improved the use of the data and revealed interactions in different subgroups in this study.

Several possible limitations of the present study should be considered: (1) This was a cross-sectional study. Thus, we could not exclude a causal relationship from the findings of this study. (2) In this study, our research subjects were members of the general population attending a medical screening center in Japan. Therefore, there is a certain deficiency in the universality and extrapolation of research. (3) In this study, our research subjects were mainly prediabetic individuals. Therefore, if the scope of the population is expanded and the diabetes sample size is increased, the results obtained will be more persuasive. Despite these potential limitations, this analysis adds to the body of knowledge regarding the effect of HbA1c on the risk of WMLs by quantifying the dramatic impact of HbA1c in women after accounting for other known WML risk factors.

Perspectives And Significance

This study highlights sex differences in the association between cerebral WMLs and HbA1c. Women had a much higher odds ratio of cerebral WMLs associated with HbA1c than men in higher HbA1c group. These findings suggest that more careful glycemic control may be needed in women with hyperglycemia to prevent cerebral WMLs. Sex differences should be taken into consideration in assessing the association between HbA1c and cerebral WMLs.

Methods

Data source

The secondary data were obtained from the DATADRYAD database (www.Datadryad.org). Users are permitted to download raw data freely from this website. According to the Dryad Terms of Service, we cited the Dryad data package in the present study. (Dryad data package: Shinkawa, Yuya et al. (2019), data from: Mathematical modeling for the prediction of cerebral WMLs based on clinical examination data, Dryad, Dataset, <https://doi.org/10.5061/dryad.73bh2q8>). The target independent variable was HbA1c level obtained at baseline, and the outcome variable was cerebral WMLs. Covariates involved in this study included PS (carotid plaque score), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), LDL cholesterol (LDL), HDL cholesterol (HDL), LH ratio (quotient of LDL and HDL), triglyceride (TG), blood glucose level (BS), plaque number (n-plaque), age, sex, smoking habit (Smoke), metabolic syndrome (Met-syn), medication to reduce blood pressure (Med-BP), medication to reduce blood sugar or insulin injection (Med-sugar), medication to reduce the level of cholesterol (Med-cho), amount of drinking per day (Drink-V), and drinking habit.

Study population

Shinkawa Yuya et al. completed the entire study. The specific details are described in the original report by Shinkawa Yuya²⁴. Participant data were nonselectively and consecutively collected from subjects who

underwent brain MRI and blood tests during the brain dock course of a comprehensive medical checkup some time between April 1, 2016, and October 31, 2017, at Shin Takeo Hospital. A total of 1904 participants, including 988 men and 916 women, were involved in this study. The data in the database were anonymous for the purpose of protecting participant privacy. Data are stored in an electronic data acquisition system. Participants' informed consent was not required in this study because of the nature of the retrospective cohort study. This study was approved by the ethical review committee of Shin Takeo Hospital.

Ethical approval. This analysis is based on summary statistics obtained from previously published analyses and therefore we have not sought additional ethical approval. All methods were performed in accordance with the relevant guidelines and regulations. Due to the retrospective nature of the study design and anonymous data collection, written informed consent was waived by the ethical review committee of Shin Takeo Hospital.

Variables

HbA1c was measured at baseline and recorded as a continuous variable. The blood and biochemical indexes were detected by the laboratory test systems C8000 (Canon Medical Systems Corporation, Tochigi, Japan) and Acute (Canon Medical Systems Corporation, Tochigi, Japan), respectively. HbA1c was measured with an automated glycohemoglobin analyzer HA8181 (Arkay Inc., Kyoto, Japan).

The outcome variable (dichotomous variable) was determined according to published guidelines and studies. Head magnetic resonance imaging (MRI) scans were acquired on MAGNETOM Symphony (Siemens Healthineers Japan, Tokyo, Japan) and MAGNETOM ESSENZA (Siemens Healthineers Japan, Tokyo, Japan) scanners. The detailed process of definition of cerebral WMLs is described as follows: there are periventricular or deep white matter lesions on FLAIR sequence of MRI (dichotomous variable: 1 = presence of cerebral white matter lesions on MRI; 0 = absence of cerebral white matter lesions on MRI).

The variables in this study can be divided into three types: (1) demographic data; (2) variables that can affect HbA1c or cerebral WMLs reported by previous literature; and (3) variables based on our clinical experiences. We selected these covariates on the basis of their association with the outcomes or a change in effect estimate of more than 10%. Therefore, the following variables were used to construct the fully adjusted model: (1) continuous variables: HDL, LDL, TG, SBP, DBP, BMI, PS, and BS (obtained at baseline); (2) categorical variables: age, sex, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce the level of cholesterol, drinking habit (every day, sometimes, or rarely drink (cannot drink)) (obtained at baseline) and plaque number. Binary variables take a value of 0 or 1 to indicate the absence or presence of some categorical effect, respectively, e.g., sex: $X = 0$ for men and $X = 1$ for women; medication to reduce blood pressure: $X = 0$ for "No" and $X = 1$ for "Yes"; medication to reduce blood sugar or insulin injection: $X = 0$ for "No" and $X = 1$ for "Yes"; medication to reduce blood pressure: $X = 0$ for "No" and $X = 1$ for "Yes". For the purpose of fully adjusting variables, we converted age from a categorical variable to a continuous variable.

Statistical analysis

Quantitative continuous variables are presented as the mean \pm standard deviation (normal distribution), and categorical variables are presented as the number and percentage. We used χ^2 (categorical variables) or Student's T test (normal distribution) to test for differences among men and women in different HbA1c groups (clinical cut point). The data analysis process of this study was based on three criteria: (1) what is the relationship between HbA1c and cerebral WMLs (linear or nonlinear) in men and women? (2) which factors modify or interfere with the relationship between HbA1c and cerebral WMLs in men and women? and (3) after adjustment for the interfering factors or after the stratified analysis, what is the true relationship between HbA1c and cerebral WMLs in men and women? Therefore, data analysis can be summarized in three steps. Step 1: Univariate and multivariate binary logistic regression were employed. We constructed two models: model 1, minimally adjusted model, adjusted only for age; model 2, fully adjusted model, adjusted for those covariates as just described. Step 2: To address the nonlinearity of HbA1c and cerebral WMLs, a generalized additive model and smooth curve fitting (penalized spline method) stratified by sex were conducted. If there is a nonlinear relationship, a recursive algorithm is used to calculate the inflection point, and then two-piecewise binary logistic regression on both sides of the inflection point is constructed. The log likelihood ratio test was used to determine the most suitable model for fitting the association between the independent variable and outcome variable. Step 3: In view of the difference in association between HbA1c and cerebral WMLs in men and women reflected by smooth curve fitting, we performed an interaction test between HbA1c and sex in different HbA1c groups. All analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and Empower Stats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). P values less than 0.05 (two-sided) were considered statistically significant.

Abbreviations

LDL: low-density lipoprotein; HDL: high-density lipoprotein; LH: quotient of LDL and HDL; TG: triglyceride; BS: blood glucose level; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; PS: carotid plaque score; Met-syn: metabolic syndrome; Med-bp: medication to reduce blood pressure; Med-sugar: medication to reduce blood sugar or insulin injection; Med-cho: medication to reduce the level of cholesterol; Drink-V: amount of drinking per day; WMLs: white matter lesions

Declarations

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Author contributions statement

HL and JY contributed to the drafting of the manuscript, and analysis and interpretation of the data. SG contributed to the conception and critical revision of the manuscript, analysis and interpretation of the data and approved the final version of the submitted manuscript. Both authors read and approved the final manuscript.

Additional information

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Figures

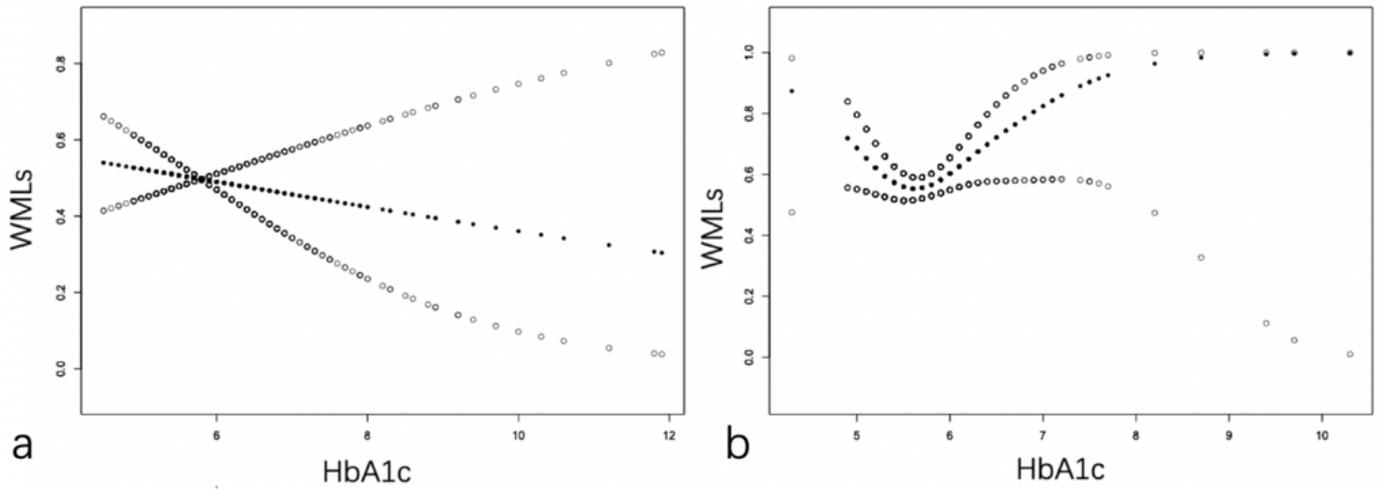


Figure 1

Smooth curve fitting of HbA1c and cerebral WMLs for men and women. A linear relationship between them was detected in men after adjusting for age, HDL, LDL, TG, DBP, SBP, BMI, BS, PS, drinking habit, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce cholesterol, and n-plaque (a). A nonlinear relationship between them was detected in women after adjusting for age, HDL, LDL, TG, DBP, SBP, BMI, BS, PS, drinking habit, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medication to reduce cholesterol levels, and n-plaque (b).