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Research Article

Sex Differences in the Association between Hemoglobin A1c and Cerebral White Matter Lesions in the General Japanese Population

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The influence of diabetes and associated sex differences on cerebral white matter lesions (WML) 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 WML 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 WML was detected in men. Fully adjusted binary logistic regression showed no association of HbA1c with cerebral WML in men. A nonlinear relationship between HbA1c and cerebral WML 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 WML 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 WML in women than in men was found in the higher HbA1c group.

1. 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 diseases [3–6]. More recent investigations have shown considerable sex differences associated with diabetes risk factors, hormonal effects on glucose, and diabetic vascular and nonvascular outcomes [7–9]. 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 complications [10–12]. Cerebral WML are mainly chronic ischemic lesions caused by small vessel diseases, which show white matter hyperintensities 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 signs [13]. Many factors have been found to be related to cerebral WML, such as age, hypertension, dyslipidemia, smoking, and various biomarkers of vascular disease [14]. Although DM is well-known as a vascular risk factor, the relationship between DM and cerebral WML is still controversial [15–18]. Prediabetes was also shown to be associated with brain structural abnormalities [19]. 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 WML [20–22]. However, such conclusions were not confirmed by another study conducted in a larger cohort of patients [23]. In addition, the sex differences in the relationship between HbA1c and cerebral WML have still not been illuminated in previous studies.

In this study, a secondary data analysis was performed using existing data from a published paper [24]. In the secondary analysis, the independent variable and dependent variable were HbA1c level and cerebral WML, 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 WML in the general population.

2. Results

2.1. 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. Women had higher values for age and high-density lipoprotein cholesterol (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 WML (yes). The opposite patterns were observed in quotient of low-density lipoprotein cholesterol (LDL) and HDL (LH), triglyceride (TG), blood glucose level (BS), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), plaque score (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 ($n > = 1$), and cerebral WML (no) in the lower 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 WML (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 ($n > = 1$), and cerebral WMLs (no).

2.2. Univariate Analysis. We listed the results of univariate analyses, adjusting for age, for men and women in Figure 1. By univariate binary logistic regression adjusting for age, we found that PS, SBP, DBP, BMI, metabolic syndrome (reserve and yes), medications to reduce blood pressure, medications to reduce sugar or insulin injection, medications to reduce the level of cholesterol (yes), and drinking habit (sometimes and everyday) were positively correlated with cerebral WML in men. By univariate binary logistic regression adjusting for age, we found that PS, HDL, SBP, DBP, medication to reduce blood pressure (yes), and plaque number ($n > 2$) were positively associated with cerebral WMLs in women. In contrast, univariate analysis showed that the amount of drinking per day (>360 ml) was negatively associated with cerebral WMLs in women.

2.3. Results of Unadjusted and Adjusted Binary Logistic Regression

2.3.1. 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 (Figures 2(a) and 2(b)). The smooth curve and the results of the generalized additive model showed a linear association of HbA1c with cerebral WML in men after adjusting for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications 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 WML (univariate and multivariate binary logistic regression). Binary logistic regression showed that there was no association of HbA1c with cerebral WML in men. The effect sizes (OR) and 95% confidence intervals are listed in Table 2. 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 WML. The smooth curve and the results of the generalized additive model showed that the relationship between HbA1c and cerebral WML was nonlinear in women after adjusting for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications 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.

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 WML 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 3).

2.3.2. Interaction Test. We used sex as the stratification variable to observe the trend of effect size in this variable (Table 4). We noted that there was an interaction between sex and HbA1c based on our a priori specification in the higher HbA1c group (HbA1c > = 5.7 mmol/L) (P value 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 1: Baseline characteristics and levels of cerebral white matter lesion risk factors by sex in the general Japanese population.

	HbA1c < 5.7 (%)			HbA1c > = 5.7 (%)		
	Men ($n = 527$)	Women ($n = 408$)	P value	Men ($n = 461$)	Women ($n = 508$)	P value
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%)	
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
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.

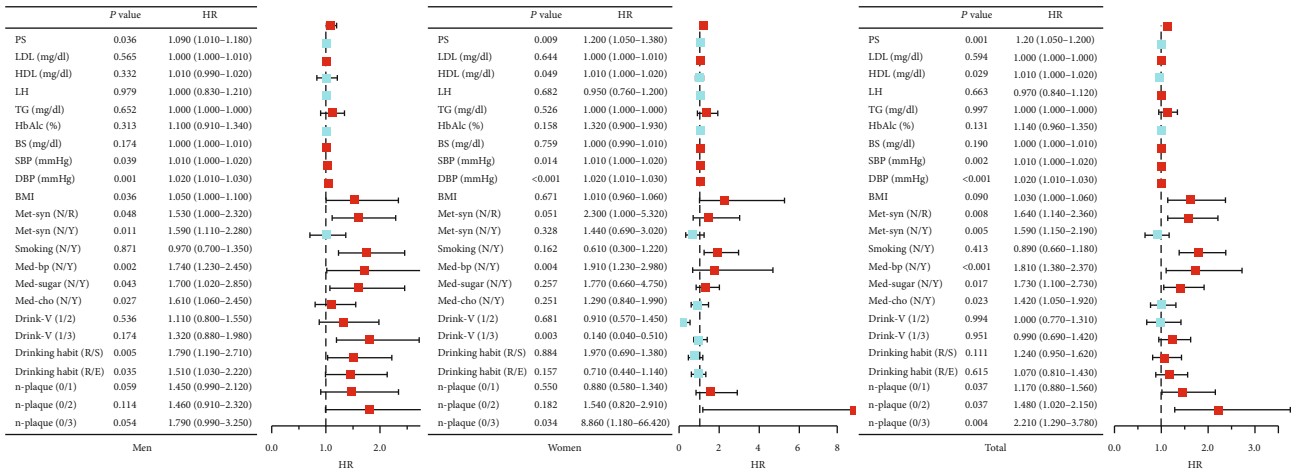


Figure 1: Forest plot. The results of the univariate analysis, adjusting for age, relationship between HbA1c and cerebral WMLs. Abbreviations: LDL, low-density lipoprotein; HDL: high-density lipoprotein; LH: quotient of LDL and HDL; TG: triglyceride; BS: blood glucose level; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; PS: carotid plaque score; Met-syn (N/R): metabolic syndrome (no versus reserve); Met-syn (N/Y): metabolic syndrome (no versus yes); Med-bp (N/Y): medication to reduce blood pressure (no versus yes); Med-sugar (N/Y): medication to reduce blood sugar or insulin injection (no versus yes); Med-cho (N/Y): medication to reduce the level of cholesterol (no versus yes); Drink-V: amount of drinking per day; drinking habit (R/S): drinking habit (rarely versus sometime); drinking habit (R/E): drinking habit (rarely versus every day); HR: hazard ratio.

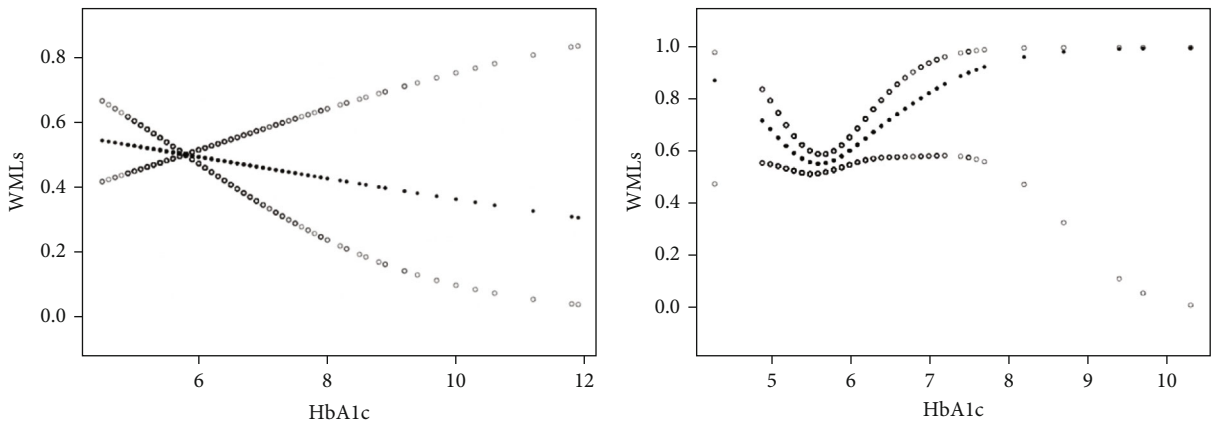


Figure 2: Smooth curve fitting of HbA1c and cerebral WMLs for men and women. A linear relationship between them was detected in men after adjusting for age, HDL, LDL, TG, DBP, SBP, BMI, BS, PS, drinking habit, metabolic syndrome, medication to reduce blood pressure, medication to reduce blood sugar or insulin injection, medications 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, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications to reduce cholesterol levels, and n-plaque (b).

Table 2: 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, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications to reduce cholesterol levels, and n-plaque.

3. Discussion

In this population-based retrospective cohort study, we found that there was no association of HbA1c with cerebral WML in men. Our findings indicate a nonlinear relationship between HbA1c and cerebral WML 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 WML 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

Table 3: The results of the one linear regression and two-piecewise linear regression model in women.

For exposure: HbA1c	
For outcome: WML	
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 WML, Cause: HbA1c. We adjusted for age, HDL, LDL, TGs, DBP, SBP, BMI, BS, PS, drinking habits, metabolic syndrome, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, and medications to reduce cholesterol and n-plaque levels.

Table 4: Effect size of HbA1c on cerebral white matter lesions in subgroups stratified by sex and HbA1c.

Model	Men (OR, 95% CI, *P*)	Women (OR, 95% CI, *P*)	*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 interaction terms for age. Model II: adjusted for age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications 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, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications to reduce the level of cholesterol, drinking habits, plaque number, and interaction terms for following variables: age, PS, LDL, HDL, TG, BS, SBP, DBP, BMI, metabolic syndrome, medications to reduce blood pressure, medication to reduce blood sugar or insulin injection, medications to reduce the level of cholesterol, drinking habits, and plaque number.

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 WML in different populations. The results of this study found a stronger association between HbA1c levels and cerebral WML 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 WML have not yet been illuminated. Over the last few years, many studies concentrating on the possible determinants of cerebral WML have suggested chronic ischemic pathogenesis in the development and progression of WML. Among the many vascular risk factors possibly implicated in the pathogenesis of cerebral WML, type 2 diabetes mellitus has been a strong risk factor. Studies have shown that structural brain abnormalities already occur in prediabetes as well as diabetes [19]. Nearly half of previous studies reported a statistically significant association between diabetes mellitus and cerebral WML, while the others reported the opposite [15]. A study by Saczynski et al. showed that participants with type 2 diabetes had a higher percentage of WML after adjustment for demographic and cardiovascular risk factors in a sample of 4415 participants [28]. van Agtmaal et al. suggested that prediabetes and type 2 diabetes were associated with larger white matter hyperintensities [19]. Similar findings were also reported in studies by Espeland et al. and Ropele et al. [29, 30]. However, there are some other studies that are inconsistent with those above. 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 mellitus [31]. A study by Moran et al. showed that type 2 diabetes mellitus was not associated with microbleeds or white matter hyperintensities (WMHs) [16]. A large-scale systematic review considered imaging methods with different sensitivities used to study the extent of WML, which may contribute to the inconsistency in conclusions on the association between DM and WML [15]. 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 WML; 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, a previous study has confirmed that these variables are related to HbA1c or cerebral WML [32].

Our study showed that a higher level of HbA1c has a greater impact on women's risk for WML than on men's risk. The inflection point of the U shape on the independent association between HbA1c and cerebral WML 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 WML, which indicates that hypoglycemic conditions may also contribute to the development of cerebral WML. 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 men [33]. Several studies supported that women underwent more pronounced exposure to hazardous metabolic risk factors than men before the onset of type 2 diabetes [34–37]. 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 men [38]. 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 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 men [41]. 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 social 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 WML 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 WML 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 WML 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 WML.

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 is 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 confirm 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 WML by quantifying the dramatic impact of HbA1c in women after accounting for other known WML risk factors.

4. Perspectives and Significance

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

5. Methods

5.1. Data Source. The secondary data were obtained from the DATADRYAD database (http://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 et al. [24], data from mathematical modeling for the prediction of cerebral WMLs based on clinical examination data, Dryad Dataset, doi:10.5061/dryad.73bh2q8). The target independent variable was the 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.

5.2. Study Population. Shinkawa et al. completed the entire study. The specific details are described in the original report by Shinkawa et al. [24]. 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 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.

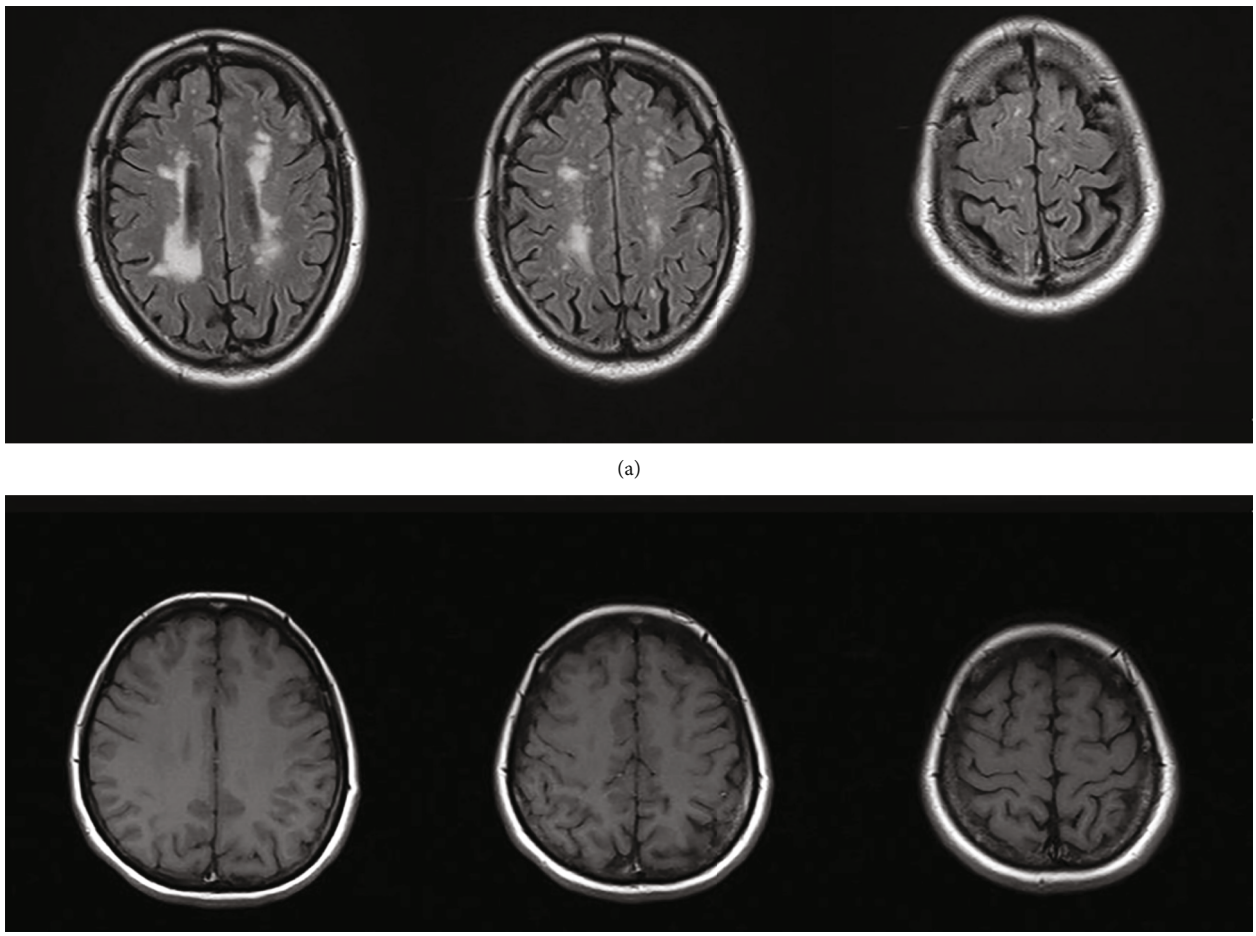
5.2.1. Ethical Approval. This analysis is based on summary statistics obtained from previously published analyses, and therefore, we have not sought additional ethical approval. All methods were performed in accordance with the relevant guidelines and regulations. Due to the retrospective nature of the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

5.3. 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 (Arkray 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). Figure 3 shows some typical head MRI examples of the presence or absence of white matter lesions [24].

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, medications to reduce blood pressure, medications to reduce blood sugar or insulin injection, medications 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 fully adjusting variables, we converted age from a categorical variable to a continuous variable.

5.4. Statistical Analysis. Quantitative continuous variables are presented as the mean ± standard deviation (normal distribution), and categorical variables are presented as number and percentage. We used $\chi 2$ (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, the data analysis can be summarized in three steps. Step 1: Univariate and multivariate binary



(a)

(b)

Figure 3: Typical examples of the presence or absence of cerebral white matter lesions. (a) Subjects with cerebral white matter lesions and (b) subjects without cerebral white matter lesions [24].

logistic regression were employed. We constructed two models: model 1, a minimally adjusted model, adjusted only for age; model 2, a 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 the outcome variable. Step 3: In view of the difference in the association between HbA1c and cerebral WML 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:	Medications to reduce blood pressure
Med-sugar:	Medications to reduce blood sugar or insulin injection
Med-cho:	Medications to reduce the level of cholesterol
Drink-V:	Amount of drinking per day
WML:	White matter lesions.

Data Availability

All data can be downloaded from the DATADRYAD database (http://www.Datadryad.org).

Disclosure

A preprint has previously been published in Research Square [42].

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

HL and JY contributed to the drafting of the manuscript and the 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. Honghao Li, Jing Yu, and Shougang Guo contributed equally to this work.

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