Visit-to-Visit Variations in Fasting Plasma Glucose and HbA_{1c} Associated With an Increased Risk of Alzheimer Disease: Taiwan Diabetes Study

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OBJECTIVE

The relationship between glycemic variability and the incidence of Alzheimer disease (AD) in patients with type 2 diabetes mellitus (T2DM) is unclear. The aim of this study was to examine visit-to-visit variations in fasting plasma glucose (FPG) and glycated hemoglobin (HbA_{1c}) represented by the coefficient of variation (CV) and to determine whether they were independently associated with AD, irrespective of HbA_{1c} and other traditional risk factors in such patients.

RESEARCH DESIGN AND METHODS

Patients with T2DM enrolled in the National Diabetes Care Management Program, age ≥60 years, and without diagnosis of AD (n = 16,706) were included in the study. Potential risk factors were analyzed using extended Cox proportional hazards regression models for competing risk of mortality on AD incidence.

RESULTS

During a median follow-up of 8.88 years, 831 incident cases of AD were identified, with a crude incidence rate of 3.5/1,000 person-years. After adjustment for sociodemographic factors, lifestyle behaviors, diabetes-related variables, FPG and HbA_{1c}, drug-related variables, and comorbidities, both FPG CV and HbA_{1c} CV were found to be significant predictors of AD, with corresponding hazard ratios of 1.27 (95% CI 1.06–1.52) for the third tertile in FPG CV and 1.32 (95% CI 1.11–1.58) for the third tertile in HbA_{1c} CV.

CONCLUSIONS

FPG CV and HbA_{1c} CV are independently associated with AD. The associations between glycemic variability and AD demonstrated in this study suggest a linked pathophysiological mechanism, which is worthy of further investigation. Further research is required to confirm our results and to evaluate whether FPG CV and HbA_{1c} CV can be valuable therapeutic targets for patients with T2DM at risk.

Alzheimer disease (AD) is a neurodegenerative disorder that accounts for more than 50% of all cases of dementia (1). Though some treatments may temporarily improve symptoms, disease-modifying therapies are still lacking, which makes the discovery of modifiable risk factors an essential therapeutic goal and the top issue for AD research (2).

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Type 2 diabetes mellitus (T2DM) is believed to be associated with stroke, eventually leading to vascular dementia, and numerous studies have established that T2DM is also a risk factor for AD (2–4). To date, cognitive dysfunction and any kind of dementia have not been targeted by current management strategies for T2DM (5). However, with rising incidence and increased life expectancy of people living with T2DM, the number of patients with T2DM who also have AD is increasing. Thus, more investigation into the identification of risk factors for AD among patients with T2DM is warranted.

Previous studies have indicated that some potential T2DM-associated risks are also associated with the risk of AD, including obesity, hypercholesterolemia, hypertension, diabetes duration, and glycemic control trajectories (6). Recent evidence suggests that glycemic variability, possibly superimposed on glycated hemoglobin (HbA_{1c}), affects the risk of developing diabetes complications (7–9). Among prior studies exploring the associations between glucose variability and diabetes complications, glucose variability in HbA_{1c} was associated with increased risks of diabetic retinopathy progression, cardiovascular events, and mortality (10) and fasting plasma glucose (FPG) variability was associated with all-cause mortality (11). In addition, HbA_{1c} variability has been shown to be a significant predictor of microalbuminuria, after ruling out the effect of mean HbA_{1c} (12), and both variation in HbA_{1c} and variation in FPG have been shown to be associated with diabetic nephropathy (13,14). In basic research settings, and even in human experimental settings, studies confirm that oscillating glucose levels have a greater effect on endothelial function and oxidative stress generation than sustained high glucose levels (15–19). It was reported that trajectories in HbA_{1c} over time were associated with cognitive function (6). Whether glycemic variability is associated with an increased risk of AD has not been explored in large-scale studies. Assessment of glycemic variability is complex, and to date, no gold standard exists to assess glycemic variability perfectly. One point-counterpoint article cited coefficient of variation (CV) and mean absolute glucose change as better markers for glycemic variability (20). Under guidelines of diabetes care with follow-up measurements for FPG and HbA_{1c}, using CV to measure glucose variation in clinical practice is more feasible than those more complex methods. In addition, CV has no dimension that can be compared among different indicators with various units, while mean absolute glucose change does not have this benefit. Therefore, we have conducted a large retrospective cohort study to examine whether FPG CV and HbA_{1c} CV have a significant and independent association with AD in patients with T2DM.

RESEARCH DESIGN AND METHODS

Study Population

The Taiwan Diabetes Cohort Study is a population-based retrospective cohort study of 63,084 Chinese patients with T2DM who were enrolled in the National Diabetes Care Management Program (NDCMP) in Taiwan from 2002 to 2004. NDCMP is a case-management program set up by the National Health Insurance (NHI) Bureau in 2002. The aim of this program was to enhance the quality of diabetes care by increasing the frequency of monitoring and providing continuity of care to decrease diabetes-related complications. All patients with a clinically confirmed diagnosis of diabetes based on criteria of the American Diabetes Association (ICD-9, Clinical Modification [ICD-9-CM], diagnosis code 250) were recruited (n = 68,034) (Fig. 1). Patients with type 1 diabetes (ICD-9-CM code 250.x1/x3) (n = 2,018) or AD (ICD-9-CM code 290.0, 290.10–290.13, 290.20, 290.21, 290.3, and 331.0) (n = 398) as well as those aged <60 years at baseline (n = 28,271) were excluded for noneligibility. We further excluded patients with <1 year of follow-up to rule out the possibility of reverse causality (n = 890) and with fewer than two records of blood biochemical measurements within 1 year after enrollment for calculation of glucose variability (n = 12,177). After additional exclusion of patients with missing data (n = 2,534) on sociodemographic factors (n = 7), insured

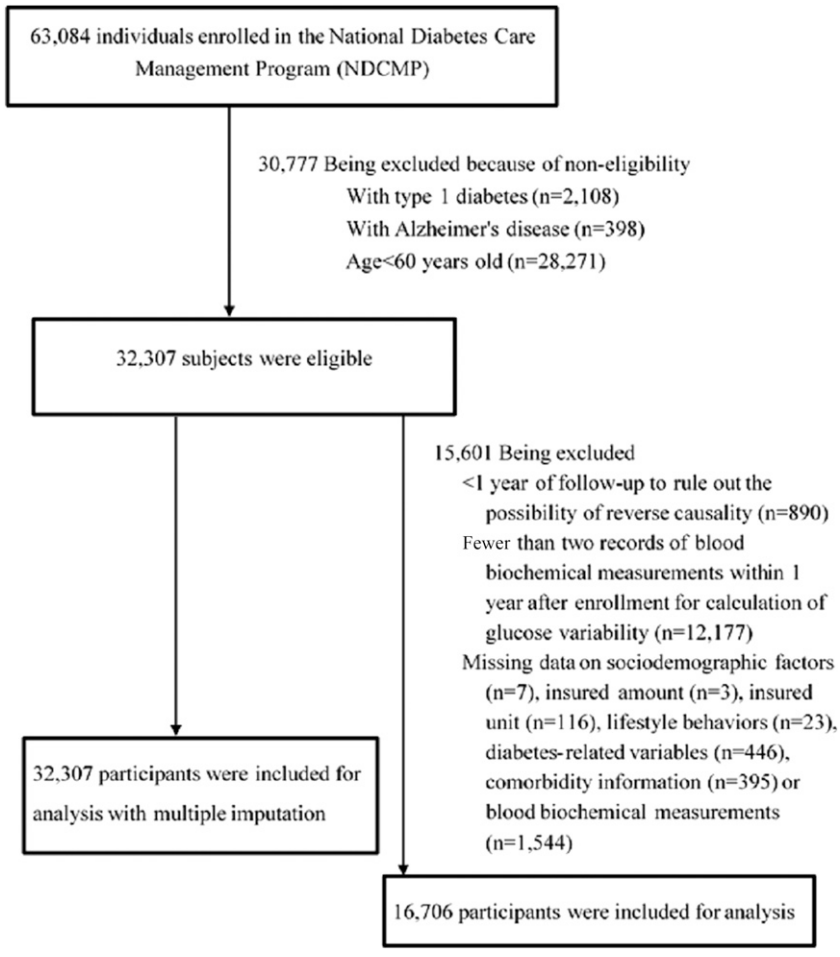

Figure 1—Flowchart of recruitment procedures for the current study. See Table 1 for breakdowns of "Insured unit" and "Insured amount."

amount (n = 3) and insured unit (n = 116) (see Table 1), lifestyle behaviors (n = 23), diabetes-related variables (n = 446), comorbidity information (n = 395), or blood biochemical measurements (n = 1,544), 16,706 subjects were included. The median follow-up period was 8.88 years (1.87 years for interquartile range). The current study was approved by the Ethical Review Board of the China Medical University Hospital.

Data Sources for Baseline and Follow-up Assessments

In March 1995, the Taiwanese government launched the NHI program. This insurance program has covered ~99% of 23.74 million people in Taiwan since 1999 (21). The NHI program covered >99.6% of the Taiwanese population, and the NHI Bureau had contracts with 100% of hospitals and 92% of clinics all over the nation in 2014 (22). To increase validity of claims data, the insurance system reviewed claim data. Every quarter, expert reviewers invited by the NHI Bureau reviewed randomly selected samples for every 50–100 ambulatory and inpatient claims in each hospital and clinic. A severe punishment was placed on every false diagnostic report. We used data sets for inpatient care by admission and outpatient care for visits during 2002–2011. Every individual had a unique personal

Table 1—Comparisons of baseline sociodemographic factors, lifestyle behaviors, diabetes-related variables, drug-related variables, and comorbidity according to AD in patients with T2DM enrolled in the NDCMP, Taiwan (n = 16,706)

	AD		
Variables	No (n = 15,875)	Yes (n = 831)	P
Sociodemographic factors			
Sex			0.003
Female	8,712 (54.88)	501 (60.29)	
Male	7,163 (45.12)	330 (39.71)	
Age (years)	69.00 ± 5.93	72.33 ± 6.17	<0.001
Amount of insured premium (NT$/month)			0.17
<17,280	5,104 (32.15)	293 (35.26)	
17,280–21,900	6,607 (41.62)	330 (39.71)	
>21,900	4,164 (26.23)	208 (25.03)	
Insured unit			0.01
Government, school employees, private enterprise employees	4,568 (28.77)	224 (26.96)	
Farmers, fishermen, and other occupations	6,747 (42.50)	328 (39.47)	
Low-income households and veterans	4,560 (28.72)	279 (33.57)	
Lifestyle behaviors			
Smoking	1,813 (11.42)	71 (8.54)	0.01
Alcohol drinking	946 (5.96)	36 (4.33)	0.06
Diabetes-related variables			
Duration of diabetes (years)	7.97 ± 7.21	9.37 ± 8.43	<0.001
Type of hypoglycemic drug use			<0.001
No medication	202 (1.27)	11 (1.32)	
One oral hypoglycemic drug	2,884 (18.17)	110 (13.24)	
Two oral hypoglycemic drugs	6,727 (42.37)	336 (40.43)	
Three oral hypoglycemic drugs	2,697 (16.99)	141 (16.97)	
>3 oral hypoglycemic drugs	729 (4.59)	50 (6.02)	
Insulin	488 (3.07)	34 (4.09)	
Insulin + oral hypoglycemic drug	2,148 (13.53)	149 (17.93)	
Drug-related variables			
Hypertension drug treatment	7,205 (45.39)	385 (46.33)	0.62
Comorbidity			
Obesity (BMI ≥27 kg/m^2)	5,446 (34.31)	234 (28.16)	<0.001
CAD	1,773 (11.17)	127 (15.28)	<0.001
CHF	547 (3.45)	44 (5.29)	0.007
Stroke	1,040 (6.55)	85 (10.23)	<0.001
Cancer	365 (2.30)	18 (2.17)	0.90
Hyperlipidemia	3,705 (23.34)	178 (21.42)	0.22
Hypertension	8,621 (54.31)	481 (57.88)	0.05
Atrial fibrillation	118 (0.74)	12 (1.44)	0.04
Chronic hepatitis	1,240 (7.81)	69 (8.30)	0.65
COPD	934 (5.88)	67 (8.06)	0.01
Hypoglycemia	82 (0.52)	10 (1.20)	0.02
Blood biochemical measurements			
Mean FPG over the first-year measurements, mg/dL	163.10 ± 47.14	168.30 ± 48.85	0.002
Mean HbA_{1c} over the first-year measurements, % (mmol/mol)	7.83 ± 1.49 (62.10 ± 16.25)	7.96 ± 1.57 (63.51 ± 17.13)	0.02

Data are n (%) or mean ± SD. NT$, New Taiwan dollars.

identification number (PIN). For security and privacy purposes, insured individuals were encrypted in the National Health Insurance Research Database (NHIRD). We used the personal PIN to interlink in all NHI datasets. NHIRD consisted of information for all insured subjects on demographic data, date and source of diagnosis, ambulatory care, inpatient admission, and outpatient/inpatient treatment. ICD-9-CM codes were used to identify individual medical status. One prior study evaluated the validity of NHIRD by discharge notes, laboratory data, and medication orders of a medical center for diagnosis of ischemic stroke and many comorbid conditions. Their findings found accuracy of ischemic stroke, acute renal failure, and diabetes was >90% and accuracy of disorder of lipid metabolism, gout, hypertension, and chronic renal failure was >80% (23). This study demonstrated that NHIRD is a valid resource for disease diagnosis. Because of the NHI program's comprehensive coverage, the proportion of enrollees withdrawing from the NHI program was very low; thus, loss–to–follow-up bias was negligible.

Upon entering NDCMP, enrollees completed a computerized, standardized questionnaire administered by a case-management nurse to record previous or current disease status, medication, and lifestyle behaviors (smoking and alcohol drinking). Enrollees also underwent a comprehensive assessment that included a series of blood tests, urine tests, eye tests, foot tests, and body measurements. After a 12-h, overnight fast, blood was drawn from an antecubital vein in the morning and sent for analysis within 4 h of collection. Each patient was followed up regularly every 3–6 months. All case subjects underwent the same tests for monitoring as they had at baseline per year of follow-up.

Outcome Ascertainment

The primary outcome was AD, as determined through linkage with inpatient and outpatient claims records in NHIRD. All AD cases were identified based on at least three service claims for ambulatory care or one service claim for inpatient care.

This study cohort was followed up from the index date to 31 December 2011 or until incident AD events, death, or withdrawal from the NHI. The index date was 1 year after baseline or entry to NDCMP. The reason why we specified the index date as 1 year after baseline instead of baseline was to rule out the possibility of reverse causality. By linking of the PIN with these computer files, 831 newly diagnosed AD patients were identified.

With use of outpatient and inpatient claims data, comorbidities were determined by at least three service claims for ambulatory care, or one service claim for inpatient care, during the 1-year period preceding cohort entry. Comorbidities included coronary artery disease (CAD) (ICD-9-CM codes 410–413, 414.01–414.05, 414.8, and 414.9), congestive heart failure (CHF) (ICD-9-CM codes 428, 398.91, and 402.x1), stroke (ICD-9-CM codes 430–438), cancer (ICD-9-CM codes 140–165, 170–175, 179–200, 202, 203, 210–213, 215–229, 235–239, 654.1, 654.10, 654.11, 654.12, 654.13, and 654.14), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), atrial fibrillation (ICD-9-CM code 427.31), chronic hepatitis (ICD-9-CM codes 571, 572.2, 572.3, 572.8, 573.1, 573.2, 573.3, 573.8, and 573.9), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–496), and hypoglycemia (ICD-9-CM codes 251.0–251.2).

Statistical Analysis

This study estimated FPG CV and HbA_{1c} CV from outpatient visits within the first year of the index date for patients with at least two FPG and HbA_{1c} records. The CV value was divided by the square root of the ratio of total visits divided by total visits minus 1 to adjust for the possibility that the number of visits may have an effect on variation (24). The χ^2 and *t* tests were used to compare differences between AD and non-AD. Cumulative incidence of AD was computed by the Kaplan-Meier method, and differences in cumulative incidence among tertile groups of FPG CV or HbA_{1c} CV were tested using a log-rank test. Cox proportional hazards models were used to evaluate the association between AD and tertiles of FPG CV or HbA_{1c} CV. A likelihood ratio test was performed to evaluate the interactions between baseline FPG and HbA_{1c} levels as well as antidiabetes treatment with FPG CV and HbA_{1c} CV on AD. The hazard ratios (HRs) and their 95% CIs were presented by multivariate adjustment. Sensitivity analysis was performed under two conditions. One was that patients with hyperglycemic hyperosmolar nonketotic syndrome (HHNK), diabetic ketoacidosis (DKA), myocardial infarction, atrial fibrillation, hypoglycemia, and stroke were excluded. The other was that a multiple imputation method was used to impute missing data. A total of 15,601 subjects were imputed for missing data of baseline characteristics and variation in HbA_{1c} and FPG. The two-tailed tests were used, and $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using SAS for Windows (version 9.4; SAS, Cary, NC).

RESULTS

The study included 16,706 participants (55.2% women and 44.8% men). There were 831 patients with AD who had T2DM. The mean number of measurements (median, minimum, maximum) for HbA_{1c} CV and FPG CV was 3.46 (3.0, 2.0, 12.0) and 3.08 (3.0, 2.0, 8.0), respectively. The crude incidence rate was 6.22/1,000 person-years (6.66 for women and 5.65 for men). Study participants were divided into tertiles of FPG CV and HbA_{1c} CV. The incidence rates per 1,000 person-years for AD were 5.20, 5.83, and 7.69 for tertiles of FPG CV and 5.25, 5.95, and 7.50 for tertiles of HbA_{1c} CV, respectively. Table 1 compares social demographics, lifestyle behaviors, medicine, and clinical factors at baseline between AD and non-AD patients. Compared with non-AD patients, AD patients were of older age, with longer duration of diabetes. A higher proportion was female, nonsmokers, persons in low-income households, and veterans; used insulin or used insulin plus oral hypoglycemic medication; were not obese; and had history of CAD, CHF, stroke, hypertension, atrial fibrillation, COPD, or hypoglycemia (Table 1).

Table 2 shows the HRs and 95% CIs of AD according to tertiles of FPG CV or HbA_{1c} CV in patients with T2DM. In age- and sex-adjusted Cox regression models, HR for AD in patients with the third tertile versus the first tertile of FPG CV was 1.64 (95% CI 1.39–1.94) and of HbA_{1c} CV was 1.60 (1.35–1.89) (model I). After multivariate adjustment, the corresponding HRs of AD for the third tertile versus the first tertile of FPG CV and HbA_{1c} CV were 1.36 (1.15–1.62) and 1.41 (1.18–1.67), respectively, when FPG CV and HbA_{1c} CV were considered separately (model III). When we simultaneously considered both HbA_{1c} CV and FPG CV, the results showed that the adjusted HRs for AD in the third tertile versus the first tertile of FPG CV

Table 2—HRs for AD according to tertiles of FPG CV or HbA_{1c} CV in patients with diabetes enrolled in the NDCMP, Taiwan (n = 16,706)

		AD (n = 831)						
					HR (95% CI)			
Variables	n	Cases	Person-years	IR	Model I	Model II	Model III	Model IV
FPG CV (%)								
≤17.4	5,519	236	45,359	5.20	1.00	1.00	1.00	1.00
17.4–34.6	5,521	261	44,784	5.83	1.11 (0.93–1.32)	1.02 (0.85–1.22)	1.02 (0.85–1.22)	1.00 (0.83–1.20)
>34.6	5,666	334	43,411	7.69	1.64 (1.39–1.94)***	1.38 (1.16–1.65)***	1.36 (1.15–1.62)***	1.27 (1.06–1.52)*
FPG (1-SD change)	16,706	831	133,554	6.22		1.12 (1.03–1.22)*	1.11 (1.02–1.21)*	1.11 (1.02–1.21)*
HbA_{1c} (1-SD change)	16,706	831	133,554	6.22		1.03 (0.93–1.13)	1.03 (0.94–1.14)	1.01 (0.92–1.12)
HbA_{1c} CV (%)								
≤8.3	5,519	237	45,122	5.25	1.00	1.00	1.00	1.00
8.3–16.3	5,513	264	44,406	5.95	1.08 (0.90–1.28)	1.02 (0.85–1.22)	0.99 (0.83–1.18)	0.98 (0.82–1.17)
>16.3	5,674	330	44,026	7.50	1.60 (1.35–1.89)***	1.46 (1.23–1.74)***	1.41 (1.18–1.67)***	1.32 (1.11–1.58)**
FPG (1-SD change)	16,706	831	133,554	6.22		1.13 (1.04–1.24)**	1.12 (1.03–1.22)*	
HbA_{1c} (1-SD change)	16,706	831	133,554	6.22		1.11 (0.92–1.11)	1.02 (0.93–1.12)	

Incidence density rate (IR) = number of incident cases/person-years × 1,000. Model I: adjusted for age and sex. Model II: adjusted for age, sex, FPG, HbA_{1c}, insured amount and insured unit (see Table 1), smoking, alcohol consumption, duration of diabetes, type of hypoglycemic drug, hypertension drug treatment, and obesity. Model III: adjusted for CAD, CHF, stroke, cancer, hyperlipidemia, hypertension, atrial fibrillation, chronic hepatitis, COPD, and hypoglycemia along with all other confounders in model II. Model IV: adjusted for PFG CV and HbA_{1c} CV along with all other confounders in model III. FPG and HbA_{1c} were measured by mean values over the first-year measurements. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

and HbA_{1c} CV were 1.27 (1.06–1.52) and 1.32 (1.11–1.58), respectively (model IV). In the final model of considering FPG and HbA_{1c} as well as FPG CV and HbA_{1c} CV simultaneously, FPG was associated with 11% increase in risk of AD for 1 SD increase in FPG. To assess whether the associations of FPG CV and HbA_{1c} CV with risk of AD vary by levels of FPG and HbA_{1c}, and medical treatment, we examined interactions among them. We did not observe any significant interaction.

In our first sensitivity analysis, we excluded patients diagnosed with potentially confounding comorbidities of HHNK (n = 326), DKA (n = 139), myocardial infarction (n = 497), atrial fibrillation (n = 130), hypoglycemia (n = 92), stroke (n = 1,125), and all comorbidities (n = 2,084) (Table 3). Results for this sensitivity analysis remained similar with little variation (HRs for the third tertile vs. the first tertile ranged from 1.25 to 1.29 for FPG CV and from 1.28 to 1.34 for HbA_{1c} CV). Similarly, the results remain significant for data with multiple imputations (Supplementary Table 2). The multivariate-adjusted HRs for the third tertile versus the first tertile of FPG CV and HbA_{1c} CV were 1.14 (95% CI 1.01–1.29) and 1.21 (1.06–1.37), respectively. Figure 2 plots AD risks for tertiles of FPG CV and HbA_{1c} CV (both log-rank test $P < 0.001$).

CONCLUSIONS

This study is the first to demonstrate that glycemic variability, determined by FPG CV and HbA_{1c} CV, was associated with AD risk in T2DM patients independently of mean FPG and HbA_{1c} and other potential risk factors during a median follow-up period of 8.88 years. These significant associations remained consistent after exclusion of potential comorbidity, demonstrating that our study results were robust.

Table 3—Sensitivity analyses for bias owing to the existence of comorbidities determined by exclusion of patients with HHNK coma, DKA, myocardial infarction, atrial fibrillation, stroke, and hypoglycemia

		AD HR (95% CI)							
		FPG CV (%)				HbA_{1c} CV (%)			
	N	1st tertile	2nd tertile	3rd tertile	P for trend	1st tertile	2nd tertile	3rd tertile	P for trend
Model I	16,380	1.00	0.98 (0.83–1.19)	1.25 (1.05–1.50)*	0.008	1.00	0.99 (0.83–1.19)	1.32 (1.10–1.58)**	0.001
Model II	16,567	1.00	1.00 (0.84–1.20)	1.26 (1.05–1.51)*	0.007	1.00	0.97 (0.81–1.16)	1.33 (1.11–1.59)**	0.001
Model III	16,209	1.00	0.99 (0.83–1.19)	1.26 (1.05–1.52)*	0.006	1.00	1.00 (0.83–1.20)	1.31 (1.09–1.57)**	0.003
Model IV	16,576	1.00	0.99 (0.83–1.19)	1.27 (1.06–1.53)**	0.004	1.00	1.00 (0.83–1.19)	1.34 (1.12–1.60)**	<0.001
Model V	16,614	1.00	0.99 (0.83–1.18)	1.27 (1.06–1.52)**	0.005	1.00	0.99 (0.83–1.18)	1.31 (1.10–1.57)**	0.002
Model VI	15,581	1.00	1.03 (0.86–1.25)	1.29 (1.07–1.57)**	0.005	1.00	1.01 (0.83–1.21)	1.33 (1.10–1.61)**	0.002
Model VII	14,622	1.00	1.01 (0.83–1.23)	1.29 (1.05–1.57)*	0.01	1.00	1.04 (0.85–1.26)	1.28 (1.05–1.56)*	0.01

The effects of FPG CV and HbA_{1c} CV were multivariate adjusted for age, sex, FPG, HbA_{1c}, insured amount and insured unit (see Table 1), smoking, alcohol consumption, duration of diabetes, type of hypoglycemic drug, hypertension drug treatment, obesity, CAD, CHF, stroke, cancer, hyperlipidemia, hypertension, atrial fibrillation, chronic hepatitis, COPD, and hypoglycemia. Model I: excluding patients with HHNK coma (n = 326). Model II: excluding patients with DKA (n = 139). Model III: excluding patients with myocardial infarction (n = 497). Model IV: excluding patients with atrial fibrillation (n = 130). Model V: excluding patients with hypoglycemia (n = 92). Model VI: excluding patients with stroke (n = 1,125). Model VII: excluding patients with HHNK, DKA, myocardial infarction, atrial fibrillation, stroke, and hypoglycemia (n = 2,084). *$P < 0.05$; **$P < 0.01$.

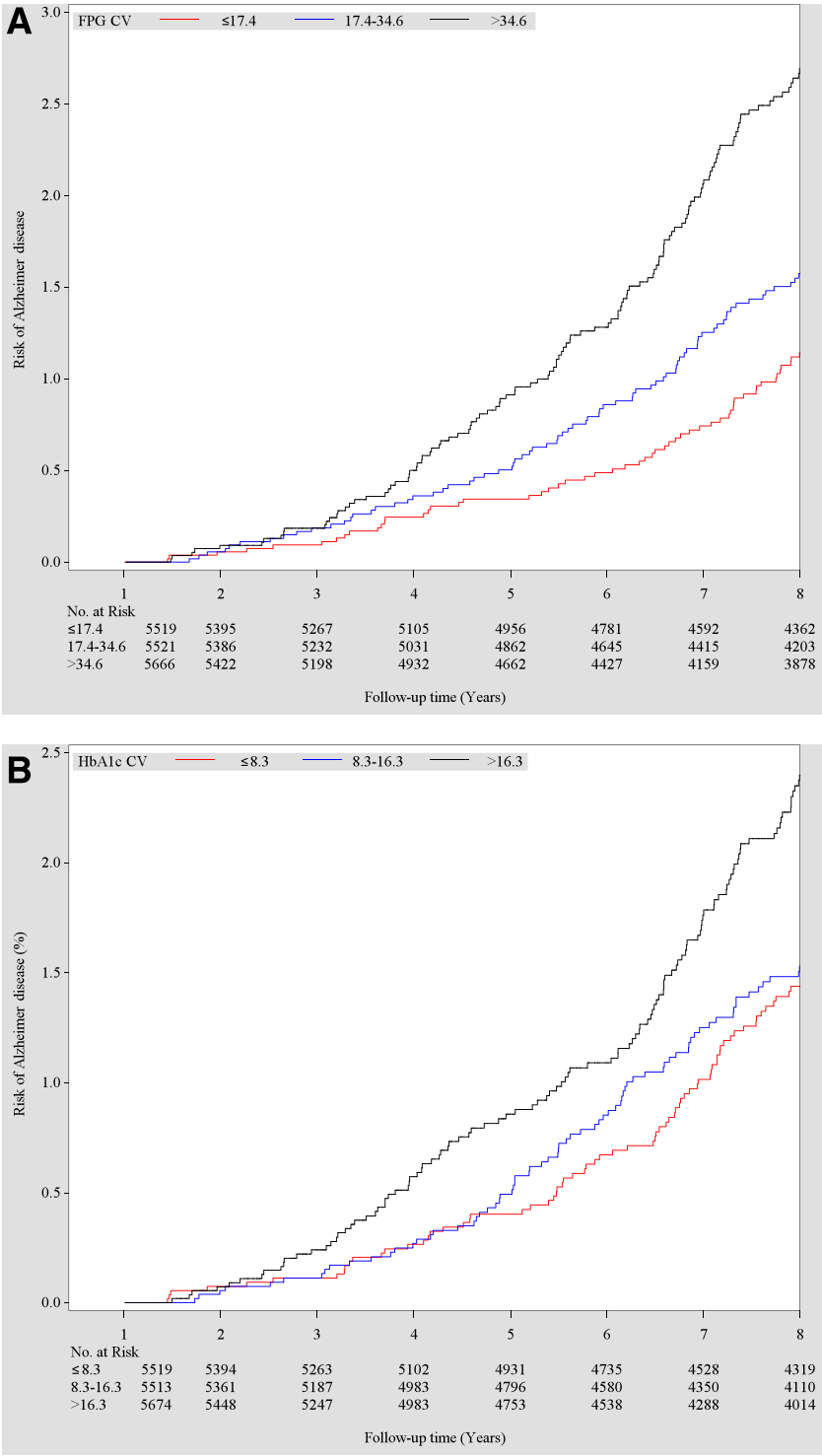

Figure 2—Risks of AD in relation to FPG CV (*A*) and HbA_{1c} CV (*B*).

The strengths of our study include a comparatively large nationwide population, standard data collection methods, a sufficiently long follow-up period, and availability of information on a large number of possible confounding factors, which further validates our study results. The findings of the current study are relevant to the clinical management of T2DM, suggesting that the stability of glycemic control can be evaluated in addition to readings of glucose levels. These findings provide new insights into glucose control and AD prevention in diabetes care for health professionals to screen patients at high risk as well as to facilitate the initiation of lifestyle modification intervention for secondary prevention. The lack of disease-modifying therapies for AD elevates the importance of discovering modifiable risk factors for AD.

The pathological hallmarks of AD are amyloid plaque and neurofibrillary tangles that damage the structure and function of neurons and synapses (1,2). However, the precise mechanisms underlying T2DM-related AD-type dementia remain to be elucidated. Several hypothetical mechanisms include impaired neurogenesis, blood-brain barrier dysfunction, inflammation, insulin resistance, vascular dysfunction, and hyperglycemia-associated products (25–29). Recently, much attention has been focused on the possibility that glycemic variability confers an additional risk for diabetes complications, independent of HbA_{1c} (9,17–19). In our study, both FPG CV and HbA_{1c} CV were significantly associated with AD in patients with T2DM. HbA_{1c} is a time-averaged mean glycemia level and is considered the "gold standard"; however, it does not reflect acute glucose fluctuation (30). On the contrary, FPG level is more likely to capture acute fluctuation in glucose level owing to lifestyle episodes, binge eating, or irregular eating. Thus, FPG might be a more sensitive indicator than HbA_{1c} for extra variation of glucose because of overindulgence in food. By similar reasoning, visit-to-visit FPG CV and HbA_{1c} CV are markers for glucose variability that capture different aspects. And this can be supported by the weak correlation between FPG CV and HbA_{1c} CV ($r = 0.32$; $P < 0.001$).

Basic research reports have also shown that HbA_{1c} variability can cause cellular "metabolic memory," insulin resistance, and deformation of the microvascular structure of the brain, which may deteriorate the clearance of amyloid plaques and increase the risk of AD (31,32). We hypothesize that glycemic variability may exacerbate dysglycemia insults, leading to induction and acceleration of AD-related pathology, and directly result in neuronal death or synaptic dysfunction other than AD pathology. However, this speculation awaits further proof, and future studies are needed to explore the precise mechanism that glycemic variability follows in the pathogenesis of AD.

Several limitations should be addressed in the current study. First, explanations for our findings were limited by the potential of

unrecognized confounding variables, such as education level, family history of AD, or apolipoprotein E4 genotype. Education is a major confounder for AD risk. Owing to lack of information on education, we cannot adjust for its confounding effect. Those patients with low educational attainment may be more likely to be diagnosed as AD or be associated with increased risk of AD (33). To adjust for the potential confounding effect of education, we considered income and occupational status, the other two indicators of sociodemographic status. Further studies considering education level are warranted to validate the results. Second, the lack of validation for the diagnosis of AD in medical records to assess the validity of AD was a concern. The diagnosis of AD is based on ICD codes, and therefore we were dependent on the diagnostic accuracy of our database. The bureau of NHI in Taiwan samples medical charts routinely and has made every effort to verify the accuracy of diagnoses in the database, which improves the accuracy of coding (34). Further, to ensure accurate diagnosis of AD, we included only those cases in which medical care was administered for AD through either outpatient visits at least three times or hospitalization at least one time. Similar methods for the identification of AD have been used in previous studies (35,36). Third, early-stage AD may also be underdiagnosed, which could result in information bias. Therefore, the risk of AD could be underestimated. This kind of underestimation might be random because there is no evidence to indicate that glycemic variability is associated with undiagnosed AD. The effect of this error may be toward the null, a lesser threat to validity. Fourth, assessment of glycemic variability is complex, and to date, no gold standard exists to assess glucose variability perfectly. Fifth, ~50% of the original cohort were included for analysis. Thus, there is potential bias from nonparticipation because of no measurement for glucose variation, missing data for covariates, or too short a follow-up period. In order to assess this potential bias, we compared standardized mean differences between those who were included and excluded. All variables had a standardized mean difference <0.1 except the category of no medication for type of hypoglycemic drug use (Supplementary Table 1), indicating a negligible difference between patients being included and excluded. In addition, our results remain similar after imputation of missing data, indicating that our findings are robust. Finally, most of the subjects in our study were Taiwanese, and generalizability of our results to other ethnic groups needs to be further confirmed.

Conclusion

We report that visit-to-visit glycemic variability, determined by FPG CV and HbA_{1c} CV, is independently associated with AD, in addition to FPG, HbA_{1c}, and other traditional risk factors, in patients with T2DM. Our findings indicate the existence of a shared pathophysiological link between glycemic variability and AD. We suggest that cognitive functions should be routinely screened in patients with T2DM, especially for those with notable glycemic variability. Further research is required to elucidate the linkage mechanisms, which could also lead to clarification of the pathogenesis of AD, and to confirm whether FPG CV or HbA_{1c} CV is a valuable therapeutic target for at-risk patients.

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