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Diabetic ketoacidosis further increases risk of Alzheimer's disease in patients with type 2 diabetes

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ABSTRACT

Aim: Diabetes mellitus (DM) is a known risk factor for dementia. It is unclear whether diabetic ketoacidosis (DKA) further increases the risk of dementia in patients with type 2 DM.
Methods: This retrospective nationwide population-based cohort study was conducted using Taiwan's National Health Insurance database. We extracted claims data for 4451 patients with type 2 diabetes and DKA and 8902 diabetic controls matched for age, gender, diabetes complication severity index, frequency of clinic visits and baseline comorbidities between 2000 and 2002. Patients with type 1 diabetes or prior hypoglycemia before index date were excluded. All patients were tracked until new dementia diagnosis, death, or end of 2011.
Results: Of the 4451 DKA patients, 211 (4.7%) and 305 (3.4%) of the 8902 diabetic controls were diagnosed as having dementia during the follow-up period. The incidence rate ratio (IRR) for dementia was 1.62 (95% CI 1.35–1.93; $P < 0.0001$) for patients with DKA versus diabetic patients without DKA. After adjusting for age, baseline comorbidities, geographic area, and income, patients with DKA were found to have 1.86 times the risk of developing dementia, compared to controls (95% CI 1.56–2.22, $P < 0.0001$). They were found to have a higher risk of Alzheimer's dementia (HR:1.86; 95% CI 1.52–2.28, $P < 0.0001$) but not non-Alzheimer's dementia.
Conclusion: Type 2 diabetes patients with DKA are at increased risk of Alzheimer's dementia but not non-Alzheimer dementia.

1. Introduction

Diabetes mellitus (DM) is a common metabolic disorder and its prevalence is increasing worldwide. It affects various body systems and causes many complications. Previous studies have found that it has an adverse effect on the cognitive system and memory disorders [1]. Dementia is the serious loss of global cognitive ability in a previously healthy person. Alzhei-

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mer's disease (AD), the leading type of dementia, accounts for 60–80% of all cases [2]. According to the World Health Organization in 2012, about thirty-five million people have dementia worldwide, and that number is expected to double every twenty years [3]. In Taiwan, according to a Nationwide Survey in 2014, the prevalence of all-cause dementia for people aged ≥65 years was 8.04%. The estimated number of people with dementia in Taiwan in 2012 was approximately 4 times that in 1992, increasing from 50,970 (3.6%) to 208,012 (8.0%) [4].

Type 2 DM increases the risk of dementia [5,6]. Many factors such as hyperinsulinemia, chronic inflammation, oxidative stress, abnormal Amyloid – β metabolism, and comorbid vascular conditions may serve as metabolic pathways linking Type 2 diabetes and Alzheimer's disease [1,7]. Many patients with type 2 diabetes have brain hypoperfusion change, which has been related to higher insulin resistance level and cognitive dysfunction [8]. In general, the longer the duration of disease and the poorer the glycemic control, the greater the risk of dementia.

Diabetic ketoacidosis (DKA), a serious acute metabolic complication of diabetes, is characterized by uncontrolled hyperglycemia, increased anion gap metabolic acidosis, and increased total body ketone concentrations [9]. Previous studies have shown that both hyperglycemia and hypoglycemia increase the risk of dementia [10,11]. In one of our previous studies, we found that DKA increased the long-term risk of stroke [12]. We did not include dementia in that study, however. Now one recent study has associated DKA with worse long-term diabetes control and impaired cognitive function in patients with type 1 DM [13]. In this study, we used a national population-based cohort to investigate whether DKA further increased the long-term risk of dementia in type 2 DM patients in Taiwan.

2. Materials and methods

2.1. Data sources

Taiwan's National Health Insurance (NHI) program covers 99% of its population of 23.3 million. Taiwan's National Research Health Institute is responsible for maintaining and managing the National Health Insurance Research Database (NHIRD), one of the largest and most complete population-based datasets in the world. This database contains detailed information on health care services provided to individual patients, including all claims for outpatient visits, hospitalizations, and prescriptions as well as basic socio-demographic information, including gender and date of birth. A claims form is filled out for each outpatient visit or hospitalization. That form contains a list of up to 3 to 5 diagnoses coded using the *International Classification of Diseases, Ninth Revision*, along with the prescription drugs and doses, procedures, and dates of these orders. In this study, we identified and collected data for diabetic patients with and without DKA from a disease-specific subset of the NHIRD, known as the Longitudinal Cohort of Diabetes Patients (LHDB). This subset contains randomized selected data (120,000 patients per year) from patients with newly diagnosed diabetes mellitus (DM: ICD9CD: 250). DM is defined in a patient in the LHDB if he or she has had at least one diagnosis of DM or a prescription for anti-diabetes medication or if he or she has had a diagnosis of DM in at least two different outpatient visits or diagnosis of DM in at least one outpatient visit in which an anti-diabetes medication was prescribed. The Institutional Review Board of Chi Mei Medical Center approved the protocol of this study. The need for informed consent was waived because the dataset analyzed in this study was devoid of any identifiable personal information.

2.2. Study sample

This retrospective cohort study followed patients who were newly diagnosed type 2 diabetes between January 1, 2000, and December 31, 2002. Those with type 1 diabetes were excluded. DKA was defined in patients if they had received a DKA diagnosis (ICD-9 code: 250.1) (DKA^+ group) during an emergency room visit or hospitalization between the date of DM diagnosis and the end of 2011.

The controls (DKA^-) were diabetic patients not diagnosed with DKA randomly selected from the LHDB and matched with cases 2:1 by index date, age of diagnosis (±30 days), duration from DM diagnosis date to DKA index date, gender, geographic area, monthly income, and selected comorbidities by propensity scoring. The index date in the DKA^+ group was the date that DKA was first diagnosed; the index date in the controls corresponded with the index date of the DKA^+ group. Patients in the control group who died before the index date were excluded. Propensity-score matching was used to reduce selection bias because it can account for the many confounding factors that may be present in an observational study with this number of variables. Propensity scores were obtained by creating a logistic regression model making the odds of diagnosis of DKA the dependent variable and the aforementioned confounding variables independent variables. Afterwards, a SAS matching macro "% OneToManyMTCH" proposed in the proceedings of the 29th SAS Users Group International (SUGI) was used. The selected comorbidities were hypertension (401–405), renal disease (582, 583, 585, 586, 588), hyperlipidemia (272.0–272.4), coronary artery disease (CAD: 410–414), stroke (430–438), depression (311, 296.2, 296.3, 300.4) and anxiety (300.1–300.3, 300.5–300.9). Any of these comorbid conditions was included if the condition was diagnosed in one inpatient or in three or more ambulatory care claims coded one year before the index medical care date. Hypoglycemia was defined in a patient if he or she had a claims record listing of one of the following ICD-9-CM codes: 251.0 (hypoglycemic coma), 251.1 (hyperinsulinism hypoglycemia) or 251.2 (unspecified hypoglycemia) within two years after index date. Patients diagnosed as having a prior hypoglycemia before index date were excluded.

2.3. Follow-up and outcome measures

The primary outcome of interest was dementia classified into three groups: (a) Alzheimer's disease and non-Alzheimer dementia, (b) Alzheimer's disease only, and (c) non-Alzheimer dementia only. We excluded patients diagnosed with Alzheimer's disease (ICD9-CM code: 290.0, 290.1, 290.2, 290.3, 294.1, 331.0) or non-Alzheimer dementia

(ICD9-CM code: 046.1, 290.4, 331.1, 331.2, 331.7, 331.8, 331.9) before the DKA diagnosis. Patients were defined as having dementia if they had at least two outpatient service claims or one inpatient service claim listing a diagnosis of dementia: Alzheimer's disease (ICD9-CM code: 290.0, 290.1, 290.2, 290.3, 294.1, 331.0) or non-Alzheimer dementia (ICD9-CM code: 046.1, 290.4, 331.1, 331.2, 331.7, 331.8, 331.9) between index date to end of 2011. Follow-up time in person-years (PY) was calculated for each person until dementia was diagnosed, death, or the end of 2011. Patients diagnosed as having a prior dementia before index date were excluded.

2.4. Statistical analyses

Standardized difference [14] was used to assess the balance of measured variables between DKA^+ and DKA^- subjects in the matched sample. A standardized difference of 0.1 or more was assumed to indicate imbalance [15]. All of the following analyses were performed using methods appropriate for the analysis of matching data when estimating the outcome effect. Incidence rate was calculated as the number of dementia cases during follow-up divided by the person-years. Incidence rate ratio (IRR) was computed using conditional Poisson regression to estimate the risk of dementia between the DKA^+ and DKA^- groups. Moreover, Cox proportional hazard regression was performed to compute the risk of dementia between the DKA^+ and DKA^- groups taking pair matching into account. The SAS procedures GENMOD (for conditional Poisson regression) and PHREG (for Cox proportional hazards regression on the matched pairs) were used to analyze matched-pair cohort data. A Kaplan–Meier survival curve was estimated in both groups, and stratified log rank test was used to compare the difference between the two cohorts using a test described by Klein and Moeschberger [16]. Moreover, subgroup analyses were performed to compare the risk of risk of dementia for DKA patients and controls by patients with and without hypoglycemia. A two-sided P value < 0.05 was considered significant. All statistical operations were performed using the SAS 9.4 statistical package (SAS Institute, Inc., Cary, North Carolina, USA).

3. Results

Table 1 shows a summary of the baseline characteristics and co-morbid medical disorders in the DKA and control groups. As can be seen in Table 2, patients with DKA had a significantly higher incidence of dementia than the controls. Of the 4451 DKA patients, 211 (4.7%) developed dementia during the follow-up period (81.63 per 10,000 person-years) and 305 (3.4%) of the 8902 controls developed dementia (50.34 per

Table 1 – Baseline demographic characteristics and comorbidities for patients with DKA and without DKA.

Characteristic	With DKA n = 4451	Without DKA n = 8902	Standardized difference
Age at DM date (years) (mean ± SD/median, IQR)	50.10 ± 15.07/48.63(21.87)	50.10 ± 14.99/48.44(21.46)	0.0000
Age at index date (years) (mean ± SD/median, IQR)	53.29 ± 15.73/51.72(22.86)	53.36 ± 15.67/51.85(22.93)	0.0045
Age at index date			
0–40	1174(26.38)	2331(26.19)	0.0043
40–60	2075(46.62)	4183(46.99)	0.0074
≥60	1202(27.01)	2388(26.83)	0.0041
Duration from DM date to index date (years) (mean ± SD/median, IQR)	3.19 ± 3.43/1.94(5.91)	3.26 ± 3.38/1.91(5.65)	0.0206
Gender			
Male	1722(38.69)	3442(38.67)	0.0004
Female	2729(61.31)	5460(61.33)	0.0004
Baseline comorbidities			
HTN	1397(31.39)	2729(30.66)	0.0158
Renal	238(5.35)	485(5.45)	0.0044
CAD	391(8.78)	782(8.78)	0.0000
Hyperlipidemia	869(19.52)	1744(19.59)	0.0018
Stroke	425(9.55)	831(9.33)	0.0075
Depression	92(2.07)	186(2.09)	0.0014
Anxiety	143(3.21)	282(3.17)	0.0023
Income (TWD)			
NT < 15840	2614(58.73)	5245(58.92)	0.0039
NT 15841 ~ 25000	1352(30.38)	2676(30.06)	0.0070
NT > 25001	485(10.90)	981(11.02)	0.0038
Area			
-North	2285(51.34)	4587(51.53)	0.0038
-Center	651(14.63)	1253(14.08)	0.0157
-South	1382(31.05)	2828(31.77)	0.0155
-East	133(2.99)	234(2.63)	0.0218

Table 2 – Risk for Dementia (Alzheimer's disease plus Non-Alzheimer dementia) in Patients with DKA and Controls.

Characteristics	Alzheimer's disease + Non Alzheimer's dementia							
	DKA			Controls			DKA vs Controls IRR (95% CI)	Adjusted HR[b] (95%CI)
	dementia	PY#	Rate[a]	dementia	PY#	Rate[a]		
All	211	25849.19	81.63	305	60590.89	50.34	1.62** (1.36–1.93)	1.86** (1.56–2.22)[c]
Age								
0–40	6	8490.62	7.07	10	18487.42	5.41	1.31(0.47–3.59)	1.00 (reference)
40–60	47	12049.9	39.00	51	27925.39	18.26	2.14** (1.44–3.17)	3.37** (1.98–5.73)
≥60	158	5308.67	297.63	244	14178.09	172.1	1.73** (1.42–2.11)	21.16** (12.67–35.34)
Gender								
Male	108	16230.19	66.54	167	38175.92	43.75	1.52** (1.19–1.94)	1.00 (reference)
Female	103	9619	107.08	138	22414.97	61.57	1.74** (1.35–2.24)	1.06 (0.89–1.27)
Comorbidity Hypertension								
Yes	113	6275.31	180.07	164	15514.1	105.71	1.70** (1.34–2.16)	1.39** (1.15–1.68)
No	98	19573.88	50.07	141	45076.79	31.28	1.60** (1.24–2.07)	1.00 (reference)
Renal disease								
Yes	15	1158.37	129.49	23	2768.85	83.07	1.56(0.81–2.99)	1.12 (0.80–1.56)
No	196	24690.82	79.38	282	57822.04	48.77	1.63** (1.36–1.95)	1.00 (reference)
CAD								
Yes	31	1823.5	170	64	4435.81	144.28	1.18(0.77–1.81)	1.22 (0.97–1.53)
No	180	24025.69	74.92	241	56155.08	42.92	1.75** (1.44–2.12)	1.00 (reference)
Hyperlipidemia								
Yes	42	4721.74	88.95	56	10524.34	53.21	1.67* (1.12–2.49)	1.06 (0.84–1.32)
No	169	21127.45	79.99	249	50066.55	49.73	1.61** (1.32–1.96)	1.00 (reference)
Stroke								
Yes	60	1613.92	371.77	59	4595.12	128.4	2.90** (2.02–4.15)	1.57** (1.26–1.94)
No	151	24235.26	62.31	246	55995.78	43.93	1.42** (1.16–1.74)	1.00 (reference)
Depression								
Yes	10	469.76	212.88	11	1203.34	91.41	2.33(0.99–5.48)	1.69** (1.09–2.64)
No	201	25379.43	79.2	294	59387.55	49.51	1.60** (1.34–1.91)	1.00 (reference)
Anxiety								
Yes	9	712.09	126.39	21	1740.12	120.68	1.05(0.48–2.29)	1.41 (0.97–2.04)
No	202	25137.1	80.36	284	58850.77	48.26	1.67** (1.39–1.99)	1.00 (reference)

* $P < 0.05$.
** $P < 0.001$.
[a] Per 10,000 person year.
[b] The model was adjusted by age, gender, hypertension, renal disease, coronary artery disease (CAD), hyperlipidemia, stroke, depression, anxiety, geographic region and income.
[c] DKA vs. controls.

10,000 person-years). The incidence rate ratio (IRR) for dementia was 1.62 (95% CI 1.35–1.93; $P < 0.0001$) for patients with DKA compared to those without DKA. In addition, elderly patients (age > 60) had 21 times the risk of dementia than younger ones (age < 40). Those with hypertension, stroke, and depression were at higher risk for dementia than the comparison group, hypertension patients having an adjusted HR (aHR) of 1.39 (1.15–1.68), stroke patients an aHR of 1.57 (1.26–1.94), and depression patients an aHR of 1.69 (1.09–2.64).

As shown in Table 3, patients with DKA had 1.86 times the risk of developing dementia than the controls (aHR: 1.86; 95% CI 1.56–2.22, $P < 0.0001$), after adjusting for age, baseline comorbidities, geographic region and income. Patients with DKA had a higher risk of Alzheimer's dementia (aHR: 2.14; 95% CI 1.75–2.62, $P < 0.0001$) but not non-Alzheimer's dementia (aHR: 1.20; 95% CI 0.83–1.71, $P = 0.3333$). Our subgroup analysis used patients with no DKA and no hypoglycemia (Table 4). Whether the DKA patients had hypoglycemia or not, they were at greater risk of dementia (aHR: 4.68 (2.20–9.93) and 1.83 (1.52–2.19), respectively).

Kaplan–Meier analysis revealed that patients with DKA had a significantly higher incidence of all dementia (log-rank test $p < 0.0001$) (Fig. 1) and Alzheimer's disease (log-rank test $p < 0.0001$) (Fig. 2) but not non-Alzheimer dementia alone (log-rank test $p = 0.7358$) (Fig. 3).

4. Discussion

In this first and largest population-based cohort study evaluating the association between DKA and risk of dementia in an Asian patients with type 2 diabetes, we found that adult diabetic patients with prior episodes of DKA had a 1.86 higher risk of dementia than our other diabetic comparison groups,

Table 3 – Risk of dementia for DKA patients and controls.

Group	Total (N)	Dementia Case (n)	Unadjusted HR (95%CI)	P-value	adjusted HR (95%CI)	P-value
Alzheimer's disease + Non Alzheimer's dementia						
DKA	4451	211	1.62(1.35–1.93)	<0.0001	1.86(1.56–2.22)	<0.0001
Non DKA	8902	305				
Alzheimer's disease						
DKA	4451	167	1.86(1.52–2.28)	<0.0001	2.14(1.75–2.62)	<0.0001
Non DKA	8902	210				
Non Alzheimer's dementia						
DKA	4451	44	1.06(0.74–1.52)	0.7359	1.20(0.83–1.71)	0.3333
Non DKA	8902	95	.			

*P-value < 0.05.
[b]The model was adjusted by age, gender, hypertension, renal disease, coronary artery disease (CAD), hyperlipidemia, stroke, depression, anxiety, geographic region and income.

Table 4 – Risk of Dementia for DKA patients with and without hypoglycemia and Controls.

Group	Alzheimer's disease + Non Alzheimer's dementia			
	Unadjusted HR (95%CI)	P-value	Adjusted HR (95%CI)	P-value
DKA, with hypoglycemia	3.43(1.62–7.26)	0.0013	4.68(2.20–9.93)	<0.0001
DKA, without hypoglycemia	1.60(1.34–1.91)	<0.0001	1.83(1.53–2.19)	<0.0001
No DKA, with hypoglycemia	4.61(1.48–14.36)	0.0085	2.25(0.72–7.08)	0.1644
No DKA, without hypoglycemia	ref.		ref.	

*P-value < 0.05.
[b]The model was adjusted by age, gender, hypertension, renal disease, coronary artery disease (CAD), hyperlipidemia, stroke, depression, anxiety, geographic region and income.

after adjusting for age, baseline comorbidities, geographic area, and income. Hypertension, stroke, and depression increased the risk of dementia.

Several previous cross-sectional and longitudinal cohort studies have found an association between hypoglycemic episodes and increased risk of dementia [17,18]. We found that patients with DKA who had hypoglycemia episodes during the follow-up period were at further increased risk of dementia. A number of mechanisms, including post-hypoglycemic neuronal damage, inflammatory processes, coagulation defects, endothelial abnormalities, and synaptic dysfunction of hippocampal neurons during hypoglycemia episodes, could be possible pathophysiological links between hypoglycemia and dementia [19]. In addition, fluctuation in blood glucose level may have played a role in development of dementia in the study. Maria Rosaria Rizzo et al., using

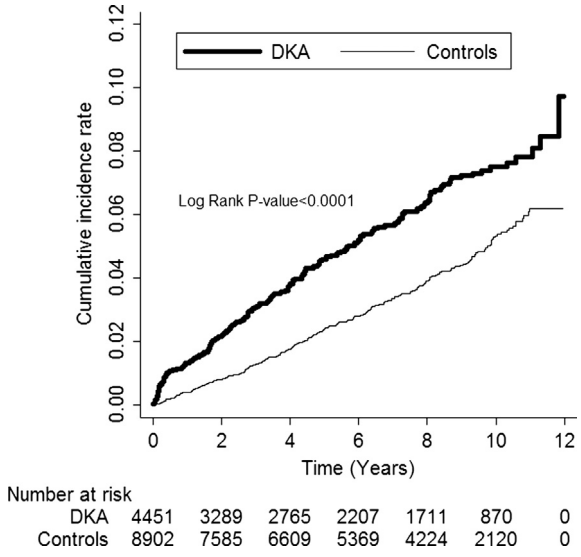

Fig. 1 – Cumulative incidence rate for all patients.

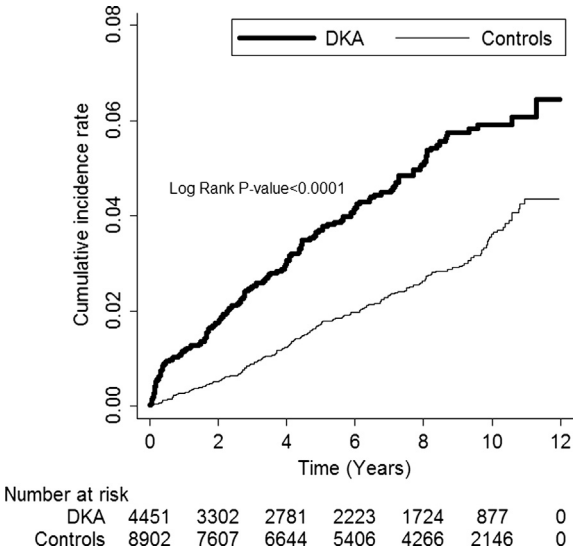

Fig. 2 – Cumulative incidence rate for Alzheimer Dementia.

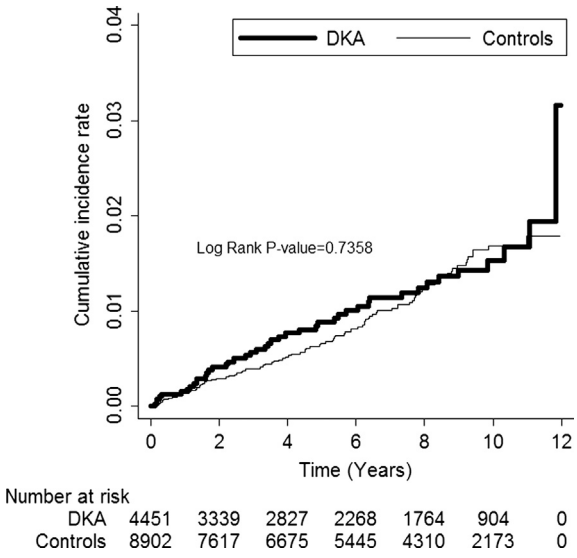

Fig. 3 – Cumulative incidence rate for non Alzheimer Dementia.

a continuous glucose monitoring system to evaluate the relationships between acute glucose fluctuations and cognitive performance in older patients with type 2 diabetes, found a significant association between glucose fluctuations and impairment of cognitive functioning independent of A1C [20].

The relationship between DKA and dementia may have different explanations. First, many cross-sectional studies agree that there is an association between the hyperglycemic state cognitive function impairment [11,21]. This impairment may occur as a result of hyperglycemica-induced oxidative stress [7]. The high osmotic stress induced by hyperglycemia disrupts the blood–brain barrier causing local leakage of vascular substances resulting in further neuronal damage [22,23]. Second, high levels of inflammation have been associated with greater risk for cognitive decline [24,25]. Chronic neuroinflammation induced by cytokines released from activated microglia and astrocytes has been identified as one mechanism underlying the initiation and progression of Alzheimer's disease [26]. DKA has been associated with a systemic inflammatory response characterized by elevation of inflammatory markers (CRP), cytokines (IL6, IL1β, TNFα), and complement activation [27,28]. Third, DKA is related to insulin deficiency, and insulin deficiency has been found to play an important role in Alzheimer's disease [5,29]. A large number of insulin receptors are found in brain areas related to memory and these receptors are also involved in the extracellular release of β-amyloid peptide. Insulin deficiency results in accumulation of β-amyloid peptide [6,30]. Patients with DKA have long been known to be insulin deficient. What was not known until this study is that they are at higher long-term risk of dementia. It should be noted, however, that the diagnosis of Alzheimer's disease is often delayed [31]. Underestimated cognitive decline could result in eating disorder and the omission of medication, promoting the development of DKA. Effective medical monitoring and comprehensive management of senile diabetic patients may help mitigate the risk of DKA [32]. The actual relationship between DKA and dementia needs to be further investigated in well-designed prospective studies.

This study also found DKA to be associated with an increased risk of Alzheimer's disease but not non-Alzheimer dementia. The reason for this difference is unknown. Vascular dementia has been found to contribute most to the development of non-Alzheimer dementia. Hypercholesterolemia, hyperglycemia, hypertension and age have been thought to risk factors of vascular dementia [33]. Further studies are needed to clarify why there is a lack of association between DKA and non-Alzheimer dementia.

This study has some limitations. First, our identification of DM, DKA and dementia were based on the diagnoses listed in an administrative database, and thus there is a possibility of recording bias. T2DM is heterogenous with regard to its clinical presentation and outcomes. New subclassifications have been proposed to better define disease progression and risk of diabetic complications [34]. Some subtypes of diabetes, including latent autoimmune diabetes in adults (LADA) and maturity onset diabetes of the young (MODY), exist and they may not have been correctly classified in this study. To maximize case ascertainment, only the patients diagnosed with DKA in an emergency department visit or a hospitalization were enrolled. Only the patients diagnosed as having dementia via neuropsychological tests (MMSE, CASI, or CDR) and brain imaging (CT or MRI) were included. Some subtle lesions may not be detected, and the definitions of Alzheimer's disease and vascular dementia have their own shortcomings. Another limitation is that some individual information, including glycaemia (as measured by HbA1c), levels of blood pressure, exercise, diet, smoking and alcohol use and medication history, was not available. To minimize selection bias, we used the propensity scores to match the comorbidities, clinical visits, and DM duration.

In conclusion, our study found increased risk of Alzheimer's disease but not non-Alzheimer dementia in type 2 diabetes patients with DKA. Patients with type 2 diabetes who had hypertension, stroke or depression were also found to be at increased risk of dementia. Clinically, it should be noted that older patients are more likely to develop DKA and thus its prevention in these patients also decreases their future risk of cognitive decline. Further research is needed to understand the mechanisms underlying the relationship between DKA and dementia.

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Conflict of interest statement

No conflict of interest is declared

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