Delirium as a Precursor to Dementia in Elderly Type 2 Diabetes Mellitus Patients

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Abstract

Purpose: This study aimed to investigate the association between delirium and incident dementia in elderly (≥65 years) type 2 diabetes mellitus (T2DM) patients, addressing the heightened dementia risk in this population.

Methods: We conducted a retrospective cohort study using data from the National Health Insurance Research Database (NHIRD) spanning January 1, 2005, to December 31, 2022. The study included elderly (≥65 years) T2DM patients newly diagnosed between January 1, 2005, and December 31, 2007. Patients were categorized into delirium and no delirium groups. A rigorous propensity score matching algorithm was applied to ensure optimal balance of baseline covariates, thereby minimizing selection bias and confounding, and Cox regression models along with competing risk analyses assessed the risk of incident dementia.

Results: The study included 5,128 elderly (≥65 years) T2DM patients, with 2,564 patients in both the delirium and no delirium groups. Baseline covariates achieved balance, including age, sex, income levels, urbanization, duration of diabetes, types of antidiabetic medications, and comorbidities. The incidence of dementia was significantly higher in the delirium group (42.75%) compared to the no delirium group (22.66%), with a *P* value <.0001. The data reveal a clear dose-response pattern, wherein each additional delirium episode substantially amplifies dementia risk, underscoring the cumulative impact of repeated episodes on cognitive deterioration: no episodes (4.40 per 100 person-years), 1 episode (7.62 per 100 person-years), and 2 or more episodes (8.41 per 100 person-years).

Conclusions: Our findings confirm a strong association between delirium and an increased risk of dementia in elderly (≥65 years) T2DM patients, suggesting a potential causal link. Effective delirium management in elderly T2DM patients is imperative to mitigate dementia risk. These findings advocate for targeted interventions to alleviate the substantial cognitive burden in this vulnerable population.

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Delirium, marked by inattention and disrupted awareness, often arises from acute events such as illness and surgery.[1,2] It is common, with a prevalence ranging from 10% to 31% among medical inpatients and up to 55% in older adults hospitalized for acute conditions.[2,3] Adverse outcomes linked to delirium include higher mortality rates, longer hospital stays, and increased admissions to residential care facilities.[2] Goldberg and colleagues'[4] meta-analysis revealed a strong association between delirium and long-term cognitive decline, even in those without preexisting cognitive impairment. However, these studies frequently did not account for key confounders or the competing risk of death.[4]

In elderly type 2 diabetes mellitus (T2DM) patients, the risks of delirium and dementia are significantly heightened.[5,6] Chronic hyperglycemia, insulin resistance, and microvascular complications contribute to this increased risk.[7] Globally, T2DM affects approximately 463 million people, projected to reach 700 million by 2045.[8] T2DM patients have a 1.5–2 times higher prevalence of dementia compared to nondiabetics.[9] Delirium prevalence is also higher in T2DM patients, further exacerbating cognitive decline.[6] The societal and economic burdens of dementia in elderly T2DM patients are substantial. Dementia results in increased healthcare utilization, long-term care needs, and significant financial costs. In the US, annual dementia care costs are estimated at $290 billion, expected to rise to $1.1 trillion by 2050.[10] T2DM-related dementia not only burdens healthcare systems but also affects the quality of life for patients and their families.[8,10]

Given the heightened vulnerability of T2DM patients to both delirium and dementia due to metabolic and vascular factors, investigating their interrelationship is of paramount importance. Gordon et al[1] explored this association in older adults using a large-scale hospital

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We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at psychiatrist.com/contact/karp, or Gary W. Small, MD, at psychiatrist.com/contact/small.

Clinical Points

- Delirium is a known risk factor for cognitive decline, and type 2 diabetes mellitus (T2DM) patients are at increased risk of both delirium and dementia. Previous studies have established the correlation between delirium and dementia but often did not account for critical confounders in elderly T2DM patients.
- This study demonstrates a significant association between delirium episodes and an increased risk of dementia in elderly T2DM patients. It also highlights a dose-response relationship, wherein multiple delirium episodes further elevate dementia risk.
- Early identification and targeted delirium management in elderly T2DM patients should be integrated into standard diabetes care protocols to mitigate cognitive decline. These findings may encourage healthcare providers to adopt early interventions targeting delirium management.

administrative dataset in New South Wales, Australia, finding that patients with delirium had a threefold higher risk of incident dementia and a 20% increased risk with each additional episode of delirium. While their study focused on the general elderly population,[1] our research specifically investigates elderly T2DM patients, providing a targeted understanding within this high-risk group. Using large-scale real-world data, we aim to clarify the strength and nature of the association between delirium and incident dementia in elderly T2DM patients without baseline dementia. By addressing this gap, we seek to inform targeted interventions to reduce the substantial burden of dementia in this growing T2DM population.

PATIENTS AND METHODS

Data Sources

We conducted a retrospective cohort study using longitudinal data from the National Health Insurance Research Database (NHIRD) from January 1, 2005, to December 31, 2022. This population-based study included newly diagnosed T2DM patients between 2005 and 2007. The NHIRD, a comprehensive repository, provides detailed information on diagnoses, procedures, medications, demographics, and integrates with Taiwan's Death Registry for accurate vital status and cause of death determination. Patient confidentiality was ensured through encrypted identifiers, and all study protocols were approved by the Institutional Review Board. Diagnoses were coded using *International Classification of Diseases, Ninth Revision (ICD-9)* or *ICD-10*, and linked data enabled robust analysis through 2022.[11–14]

Study Design and Sample

We defined a 6-year index period (January 1, 2008, to December 31, 2013) to confirm the absence of prior dementia diagnoses, calculate comorbidities, assess diabetes duration, and evaluate medication use (Table 1). Comorbidities were identified using *ICD-9* or *ICD-10* codes from the preceding 2 years. The follow-up period extended 62 months from the end of the index period to the dataset's conclusion. Dementia (*ICD-10*: F00.0–F03, F05.1, G30.0–G31.8; *ICD-9*: 290.0–290.9, 331.0–334.9) and delirium (*ICD-10*: F05.0–F05.9, R41.0; *ICD-9*: 293.0–293.9) diagnoses were extracted, with delirium episodes recorded only if acute and requiring hospitalization.

Exclusion criteria included preindex dementia or delirium diagnoses, age >110 years, and data inconsistencies. Patients were divided into delirium and no-delirium groups. For delirium patients, the first recorded episode was designated as the index episode, excluding those with prior dementia. Patients in the no-delirium group with dementia before the index episode were also excluded. A 1:1 propensity score matching approach was applied without replacement, controlling for demographic variables, diabetes severity, medication use, and comorbid conditions to minimize confounding bias. Delirium as the primary diagnosis was excluded from matching criteria.

Outcomes

The primary outcome was the occurrence of dementia. The date when a new dementia diagnosis was recorded was identified as the event time for incident dementia. Incident dementia diagnoses included *ICD-10* codes F00.1, F00.2, F00.9, G30.1, G30.8, G30.9, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, I67.3, F02.0, F02.3, F03, F05.1, G31.0, G31.1, and G31.8. Corresponding *ICD-9* codes for incident dementia were 290.0, 290.1, 290.2, 290.3, 331.0, 331.1, 331.2, 331.3, 331.4, 331.5, 331.6, 331.7, 331.8, 331.9, 332.0, 333.0, 333.1, 333.2, 333.3, 333.4, 333.5, 333.6, 333.7, 333.8, 333.9, 334.0, 334.1, 334.2, 334.3, 334.4, 334.5, 334.6, 334.7, 334.8, and 334.9.

Statistical Analysis

Descriptive statistics were calculated at baseline for the delirium and no-delirium groups and the total eligible sample. Linear associations between continuous covariates (age, Adapted Diabetes Complication Severity Index, and Charlson Comorbidity Index [CCI]) and incident dementia were assumed. Follow-up extended until dementia onset, death, or 62 months, with patients remaining event-free censored at 62 months. We assessed dementia incidence differences between the delirium and no-delirium groups. A landmarking approach evaluated the dose-response relationship between delirium episodes within the first 12 months of follow-up (categorized as 0, 1, or ≥2 episodes). Dose-response models included covariates like age and hospital episodes during the landmark period, analyzing patients who remained event-free in that period.

Table 1.

Baseline Characteristics of Type 2 Diabetes Mellitus Patients With and Without Delirium Following Propensity Score Matching

	No delirium N = 2,564		Delirium N = 2,564		
	N	%	N	%	ASMD
Age, mean ± SD, y	76.72 ± 15.45		75.57 ± 16.16		
Age, median (IQR), y	79.00 (73.00, 88.00)		79.00 (73.00, 88.00)		
Age group					.0970
65–70 y	807	31.47	924	36.04	
71–75 y	476	18.56	441	17.20	
76–80 y	784	30.58	731	28.51	
≥81 y	497	19.38	468	18.25	
Sex					.0454
Female	982	38.30	1,039	40.52	
Male	1,582	61.70	1,525	59.48	
Income level (NTD)					.0680
Low income	1,057	41.22	1,003	39.12	
≤20,000	1,263	49.26	1,272	49.61	
20,001–30,000	153	5.97	175	6.83	
30,001–45,000	63	2.46	84	3.28	
>45,000	28	1.09	30	1.17	
Urbanization					.0249
Rural	968	37.75	999	38.96	
Urban	1,596	62.25	1,565	61.04	
Duration of diabetes, mean ± SD, y	1.43 ± 1.54		1.48 ± 1.49		.0330
Duration of diabetes, median (IQR), y	1.16 (0.36, 2.18)		1.08 (0.37, 2.12)		
Duration of diabetes, y					.0313
≤1	1,182	46.10	1,222	47.66	
>1	1,382	53.90	1,342	52.34	
No. of types of antidiabetic medications					.0790
0	638	24.88	626	24.41	
1	780	30.42	716	27.93	
2	435	16.97	425	16.58	
3	382	14.90	432	16.85	
4 or more	329	12.83	365	14.24	
Antidiabetic medications					
Insulin	1,125	43.88	1,450	56.55	.2555
Metformin	1,073	41.85	1,036	40.41	.0293
Sulfonylureas	1,301	50.74	1,183	46.14	.0921
Sodium-glucose cotransporter-2 inhibitors	23	0.90	26	1.01	.0113
Alpha-glucosidase inhibitors	229	8.93	255	9.95	.0349
Glucagon-like peptide-1 receptor agonists	167	6.51	154	6.01	.0206
Dipeptidyl peptidase-4 inhibitors	309	12.05	373	14.55	.0737
Adapted Diabetes Complications Severity Index, mean ± SD	2.74 ± 1.95		2.72 ± 2.02		
Adapted Diabetes Complications Severity Index, median (IQR)	3.00 (1.00, 4.00)		2.00 (1.00, 4.00)		
Adapted Diabetes Complications Severity Index					.0620
0	433	16.89	457	17.82	
1	218	8.50	255	9.95	
2	624	24.34	621	24.22	
≥3	1,289	50.27	1,231	48.01	
Adapted Diabetes Complications Severity Index complications					
Retinopathy	266	10.37	187	7.29	.0087
Nephropathy	792	30.89	837	32.64	.0376
Neuropathy	430	16.77	388	15.13	.0448
Cerebrovascular	1,051	40.99	1,039	40.52	.0096
Cardiovascular	1,340	52.26	1,291	50.35	.0382
Peripheral vascular disease	287	11.19	250	9.75	.0470
Metabolic	198	7.72	233	9.09	.0494

(continued)

Table 1 (continued).

	No delirium N = 2,564		Delirium N = 2,564		
	N	%	N	%	ASMD
Coexisting comorbidities					
Hypertension	1,747	68.14	1,725	67.28	.0184
Hyperlipidemia	624	24.34	696	27.15	.0643
Coronary artery disease	850	33.15	822	32.06	.0233
Stroke	1,137	44.34	1,090	42.51	.0369
Depression	384	14.98	379	14.78	.0056
Anxiety	427	16.65	416	16.22	.0116
Heart failure	498	19.42	508	19.81	.0098
Peripheral vascular disease	113	4.41	115	4.49	.0039
Atrial fibrillation	210	8.19	223	8.70	.0183
Traumatic head injury	297	11.58	305	11.90	.0099
Hearing loss	62	2.42	78	3.04	.0381
Sleep disorder	15	0.59	15	0.59	.0000
Liver cirrhosis	714	27.85	736	28.71	.0191
Systemic lupus erythematosus	28	1.09	22	0.86	.0234
Parkinson's disease	153	5.97	160	6.24	.0113
Chronic obstructive pulmonary disease	892	34.79	844	32.92	.0395
Habitus					
Current smoking status	28	1.09	31	1.21	.0113
Presence of alcohol-related diseases	425	16.58	400	15.60	.0267
Concurrent medication use					
Statins	350	13.65	362	14.12	.0136
Aspirin	856	33.39	862	33.62	.0049
Charlson Comorbidity Index, mean (SD)	2.65 ± 2.04		3.20 ± 2.54		
Charlson Comorbidity Index, median (IQR, Q1–Q3)	2.00 (1.00, 4.00)		3.00 (1.00, 5.00)		
Charlson Comorbidity Index					.0569
0	341	13.30	392	15.29	
≥1	2,223	86.70	2,172	84.71	
Outcomes					*P* value
Dementia	581	22.66	1,096	42.75	<.0001
All-cause death	1,676	65.37	1,724	67.24	.2328

Abbreviations: ASMD = absolute standardized mean difference, IQR = interquartile range, NTD = New Taiwan Dollar, T2DM = type 2 diabetes mellitus.

Cox regression models assessed the impact of delirium on dementia and the competing risk of death, adjusting for confounders. Models ranged from univariable (Model 1) to fully adjusted (Model 5), incorporating variables such as age, sex, income, urbanization, diabetes duration, medication use, comorbidities, body habitus, and CCI. The Fine and Gray method estimated dementia hazard ratios (HRs) considering death as a competing risk.[15] Dementia incidence rates per 100 person-years were calculated across groups and stratified by sex.

Sensitivity analyses ensured robustness by excluding poorly matched patient pairs (top 10% of distance values) and controlling for residual differences. Additional analyses excluded patients diagnosed with dementia or deceased within 24 months of the index episode to address undetected dementia. Analyses were performed in the matched sample and stratified by sex to explore differences between men and women.

All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Sample Characteristics

Following propensity score matching, the study included 5,128 elderly T2DM patients (aged 65 years and older), with 2,564 patients in both the delirium and no delirium groups. The baseline covariates that achieved balance (absolute standardized mean difference <0.1) between these groups included age, sex, income levels, urbanization, duration of diabetes, types of antidiabetic medications, Adapted Diabetes Complications Severity Index, coexisting comorbidities, body habitus (current smoking status, presence of alcohol-related diseases), concurrent medication use, and CCI (Table 1). The age distribution was balanced between the groups, with

mean ages of 76.72 ± 15.45 years in the no delirium group and 75.57 ± 16.16 years in the delirium group.

The incidence of dementia was significantly higher in the delirium group (42.75%) compared to the no delirium group (22.66%), with a *P* value of <.0001. The incidence of all-cause death did not differ significantly between the groups (67.24% in the delirium group vs 65.37% in the no delirium group, *P* = .2328).

Dementia and Competing Risk of Death

Table 2 shows the results of Cox regression models assessing the risk of dementia and the competing risk of death in T2DM patients with delirium episodes recorded within the first 12 months of follow-up. The analyses revealed that patients with 1 episode of delirium had a significantly higher risk of developing dementia compared to those without delirium across all models. In Model 1 (univariable), the adjusted HR for 1 delirium episode was 1.72 (95% CI, 1.51–1.97, *P* < .0001), and for 2 or more episodes, the adjusted HR was 1.89 (95% CI, 1.56–2.29, *P* < .0001).

When adjusting for age and sex (Model 2), the risk increased, with an HR of 1.97 (95% CI, 1.72–2.25, *P* < .0001) for 1 episode and 2.33 (95% CI, 1.91–2.83, *P* < .0001) for 2 or more episodes. Further adjustments for income levels, urbanization, duration of diabetes, types of antidiabetic medications, and the Adapted Diabetes Complications Severity Index (Model 3) showed an HR of 1.97 (95% CI, 1.73–2.26, *P* < .0001) for 1 episode and 2.33 (95% CI, 1.92–2.83, *P* < .0001) for 2 or more episodes.

In Model 4, which included additional adjustments for coexisting comorbidities, the HR was 1.41 (95% CI, 1.20–1.65, *P* < .0001) for 1 episode and 1.67 (95% CI, 1.35–2.07, *P* < .0001) for 2 or more episodes. Model 5, which further adjusted for body habitus, concurrent medication use, and CCI, showed an HR of 1.37 (95% CI, 1.17–1.60, *P* = .0001) for 1 episode and 1.51 (95% CI, 1.22–1.87, *P* = .0002) for 2 or more episodes.

The competing risk of death analysis also indicated a significant increase in risk for patients with delirium. In Model 1, the HR for 1 episode was 2.12 (95% CI, 1.86–2.43, *P* < .0001) and 2.34 (95% CI, 1.94–2.83, *P* < .0001) for 2 or more episodes. Model 2 showed an HR of 2.39 (95% CI, 2.08–2.74, *P* < .0001) for 1 episode and 2.80 (95% CI, 2.31–3.38, *P* < .0001) for 2 or more episodes. In Model 3, the HR was 2.39 (95% CI, 2.08–2.74, *P* < .0001) for 1 episode and 2.80 (95% CI, 2.31–3.38, *P* < .0001) for 2 or more episodes. Model 4 indicated an HR of 2.28 (95% CI, 1.97–2.65, *P* < .0001) for 1 episode and 2.66 (95% CI, 2.18–3.25, *P* < .0001) for 2 or more episodes. Finally, Model 5 showed an HR of 2.23 (95% CI, 1.92–2.59, *P* < .0001) for 1 episode and 2.44 (95% CI, 1.99–3.00, *P* < .0001) for 2 or more episodes.

Incidence of Dementia in T2DM Patients with Delirium Episodes

Table 3 presents the incidence rates of dementia in T2DM patients, categorized by the presence and number of delirium episodes recorded within the first 12 months of follow-up. The analysis included 2,564 patients in both the no delirium and delirium groups. Among the delirium group, 1,832 had no additional episodes, 1,254 had 1 episode, and 318 had 2 or more episodes.

The total number of dementia events was significantly higher in the delirium group (1,096 events) compared to the no delirium group (581 events). The total person-years of follow-up were 9,066.9 for the no delirium group and 8,714.7 for the delirium group. The overall incidence rate per 100 person-years was 6.41 for the no delirium group and 12.58 for the delirium group. Within the delirium group, the incidence rates per 100 person-years were 4.40 for patients with no additional episodes, 7.62 for 1 episode, and 8.41 for 2 or more episodes.

Gender-specific analysis showed that females had higher incidence rates of dementia. For females, the incidence rates were 7.82 per 100 person-years in the no delirium group and 13.27 per 100 person-years in the delirium group. Within the delirium group, the rates were 5.12 for no additional episodes, 8.18 for 1 episode, and 10.29 for 2 or more episodes. For males, the incidence rates were 5.47 per 100 person-years in the no delirium group and 12.09 per 100 person-years in the delirium group. Within the delirium group, the rates were 3.92 for no additional episodes, 7.22 for 1 episode, and 7.86 for 2 or more episodes.

Cumulative Incidence of Dementia by Delirium Status and Episode Frequency in T2DM Patients

Figure 1 illustrates the Kaplan-Meier curve for the cumulative incidence of dementia in propensity score-matched T2DM patients with and without delirium. The curve demonstrates that patients with delirium had a significantly higher cumulative incidence of dementia compared to those without delirium. Figure 2 presents the Kaplan-Meier curve for the cumulative incidence of dementia in T2DM patients with delirium episodes recorded within the first 12 months of follow-up (landmark period). The analysis shows that the cumulative incidence of dementia increases with the number of delirium episodes, indicating a dose-response relationship.

DISCUSSION

T2DM is significantly associated with an increased risk of dementia,[5,6] primarily due to chronic hyperglycemia, insulin resistance, and microvascular complications that promote cerebrovascular dysfunction

Table 2.

Cox Regression Models Assessing Dementia and Competing Risk of Death in Type 2 Diabetes Mellitus Patients With Delirium Episodes Recorded Within the First 12 Months of Follow-Up

Dementia	Delirium episodes recorded within the first 12 months of follow-up Ref: no delirium	Adjusted HR[a] (95% CI)	*P* value	Competing risk of death analysis: Adjusted HR[b] (95% CI)	*P* value
Model 1	Delirium episodes 1	1.72 (1.51–1.97)	<.0001	2.12 (1.86–2.43)	<.0001
	Delirium episodes ≥2	1.89 (1.56–2.29)	<.0001	2.34 (1.94–2.83)	<.0001
Model 2	Delirium episodes 1	1.97 (1.72–2.25)	<.0001	2.39 (2.08–2.74)	<.0001
	Delirium episodes ≥2	2.33 (1.91–2.83)	<.0001	2.80 (2.31–3.38)	<.0001
Model 3	Delirium episodes 1	1.97 (1.73–2.26)	<.0001	2.39 (2.08–2.74)	<.0001
	Delirium episodes ≥2	2.33 (1.92–2.83)	<.0001	2.80 (2.31–3.38)	<.0001
Model 4	Delirium episodes 1	1.41 (1.2–1.65)	<.0001	2.28 (1.97–2.65)	<.0001
	Delirium episodes ≥2	1.67 (1.35–2.07)	<.0001	2.66 (2.18–3.25)	<.0001
Model 5	Delirium episodes 1	1.37 (1.17–1.60)	.0001	2.23 (1.92–2.59)	<.0001
	Delirium episodes ≥2	1.51 (1.22–1.87)	.0002	2.44 (1.99–3.00)	<.0001

[a]The Cox model, which treats metformin use as a dynamic variable, was adjusted to account for several factors: Model 1 (univariable), Model 2 (adjusted for age and sex), Model 3 (adjusted for age, sex, income levels, urbanization, duration of diabetes, types of antidiabetic medications, and Adapted Diabetes Complications Severity Index), Model 4 (adjusted for age, sex, income levels, urbanization, duration of diabetes, types of antidiabetic medications, Adapted Diabetes Complications Severity Index, and coexisting comorbidities), and Model 5 (adjusted for age, sex, income levels, urbanization, duration of diabetes, types of antidiabetic medications, Adapted Diabetes Complications Severity Index, coexisting comorbidities, habitus, concurrent medication use, and Charlson Comorbidity Index).

[b]The Fine and Gray method was adapted to estimate the hazard of dementia considering competing risks from death.

Abbreviation: HR = hazard ratio.

Table 3.

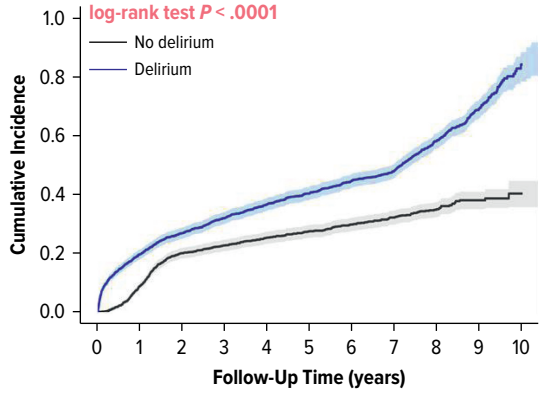
Delirium Episodes and Dementia Incidence Rates in Type 2 Diabetes Mellitus Patients

Outcome = dementia	No delirium group	Delirium group	Delirium episodes recorded within the first 12 months of follow-up: 0	1	≥2
No. of patients at risk					
Total	2,564	2,564	1,832	1,254	318
Female	982	1,039	689	513	128
Male	1,582	1,525	1,143	741	190
No. of events					
Total	581	1,096	378	516	141
Female	282	476	175	230	69
Male	299	620	203	286	72
Person-years of follow-up					
Total	9,066.9	8,714.7	8,597.2	6,772.2	1,676.8
Female	3,605.5	3,586.6	3,416.0	2,812.1	670.6
Male	5,461.4	5,128.1	5,181.2	3,960.0	1,006.2
Incidence rate per 100 person-years					
Total	6.41	12.58	4.40	7.62	8.41
Female	7.82	13.27	5.12	8.18	10.29
Male	5.47	12.09	3.92	7.22	7.86

and inflammation.[16] Epidemiological studies indicate that T2DM patients have a 59% higher risk of developing dementia than non-diabetics.[9] This increased risk stems from poor glycemic control and vascular complications.[17] Delirium is closely linked to dementia, with evidence showing that delirium significantly raises the risk of dementia while cognitive impairment predisposes individuals to delirium.[1,4] Gordon et al[1] demonstrated a causal relationship, highlighting delirium as a modifiable risk factor. Our study focuses on elderly T2DM

Figure 1.

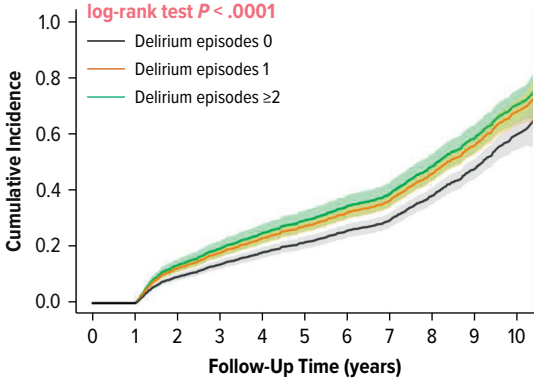
Kaplan-Meier Curve of Cumulative Incidence of Dementia in Propensity Score-Matched Type 2 Diabetes Mellitus Patients With and Without Delirium



No. at risk						
No delirium	2564	1183	955	774	324	20
Delirium	2564	1308	986	765	308	12

Figure 2.

Kaplan-Meier Curve of Cumulative Incidence of Dementia in Type 2 Diabetes Mellitus Patients With Delirium Episodes Recorded Within the First 12 Months of Follow-Up (Landmark Period)



No. at risk						
0	1832	1183	955	774	324	20
1	1254	1046	790	618	248	9
≥2	318	262	196	147	60	3

patients, a high-risk group, to explore the association between delirium and dementia, aiming to inform interventions to reduce dementia burden in this population.

Epidemiological data reveal that T2DM patients face elevated risks for both delirium and dementia.[5,6] Hospitalized T2DM patients show higher delirium prevalence, contributing to extended stays and increased costs.[18,19] Poor glycemic control, hypertension, cardiovascular disease, and nephropathy further exacerbate these risks.[1,19,20] This study highlights the strong association between delirium and dementia in elderly T2DM patients, with a dementia incidence of 42.75% in the delirium group versus 22.66% in the no-delirium group ($P < .0001$; Table 1 and Figure 1). A clear dose-dependent increase in dementia risk was identified: patients with 1 delirium episode exhibited nearly double the incidence rate compared to those without delirium (7.62 vs 4.40 per 100 person-years), while patients with multiple episodes showed an even greater risk (8.41 per 100 person-years) (Tables 2 and 3; Figure 2). These findings suggest a causal link between delirium and dementia. Identifying and managing delirium in T2DM patients may help prevent dementia, and understanding independent risk factors could guide targeted interventions to reduce dementia incidence in this high-risk population.[1]

Gordon et al[1] highlighted mortality as a significant competing risk that influences dementia onset, consistent with our findings, where all-cause death rates were high but similar between the delirium and no-delirium groups (Table 1). To confirm delirium as a risk factor for dementia, we conducted competing risk analysis (Table 2). Previous studies, such as Garcez et al[21] and Rolandi et al,[22] reported subdistribution HRs of 1.94 and 8.70, respectively, for dementia following delirium. However, their methodologies varied, and adjustments for illness severity or multiple delirium episodes were lacking.[4,21,22] In contrast, our study comprehensively adjusted for diabetes severity, comorbidities, and all dementia risk factors (Table 1). Richardson et al[23] found delirium nearly tripled dementia risk, with higher risks associated with multiple episodes. Our results align with this, but their smaller sample size and general elderly population differ from our T2DM-focused cohort. Additionally, Goldberg et al[4] noted diagnostic variability's minimal impact on study outcomes. Key differences include our focus on T2DM patients in Taiwan versus Gordon et al's[1] general elderly population in New South Wales. Despite these differences, both studies underscore delirium's role as a modifiable dementia risk factor. Our study uniquely investigates delirium's impact on diabetes-related dementia, finding that elderly T2DM patients with delirium have twice the dementia risk, which increases with episode frequency. These findings highlight the importance of managing delirium to mitigate dementia risk in high-risk T2DM populations.

Our study demonstrates a strong association between delirium and incident dementia in elderly T2DM patients, indicating a potential causal link. Delirium's effects—drowsiness, agitation, circadian disruptions, and unsafe behaviors—can lead to geriatric syndromes and

complications that harm the brain.[24] Mechanisms such as systemic and neuroinflammation may contribute to neuronal injury and neurodegeneration.[25] In T2DM, chronic hyperglycemia and insulin resistance exacerbate cerebrovascular dysfunction, inflammation, and oxidative stress, increasing dementia risk.[5,16,26] Delirium in T2DM may stem from glucose fluctuations, metabolic imbalances, and comorbidities, further impairing cognition. Our findings show a greater dementia risk increase among men with delirium compared to women, although women had a slightly higher overall dementia rate. Emerging research on sex differences in dementia suggests varying risks and neuropathological patterns.[27–30] While some meta-analyses report no significant sex differences, others highlight variations requiring further investigation. These insights underline the need for targeted, sex-specific interventions.

Pooled data indicate that multicomponent nonpharmacologic interventions reduce delirium incidence, duration, and hospital stay.[31] Programs like the Hospital Elder Life Program lower delirium rates, falls, and healthcare costs while preserving functional status.[32] However, their impact on dementia risk remains uncertain. Given the rising dementia burden, future trials should focus on assessing the benefits of delirium prevention on dementia incidence. Identifying independent risk factors for delirium-induced dementia in T2DM patients is essential for targeted interventions to reduce dementia risk in this vulnerable population.

This pioneering study addresses the heightened dementia risk in T2DM patients by adjusting for key baseline variables, accounting for the competing risk of death, and using a long follow-up period to minimize bias. The extensive dataset enabled precise dose-response analyses, while propensity score matching, multiple Cox regressions, and sensitivity analyses confirmed the robustness of the results. Gender-stratified analyses provided insights with significant clinical and pathophysiological implications.

Reliance on clinical coding for delirium and dementia may lead to misclassification, introducing potential biases. Despite supporting data, false positives and negatives remain possible. Residual confounding from unmeasured variables and the lack of data on delirium duration and severity limit our analysis to coded episodes. The association between delirium and dementia may also be influenced by factors such as frailty. While our findings suggest that delirium contributes to dementia in T2DM patients, observational study limitations prevent establishing causality. Future research should integrate multiple data sources to enhance detection accuracy and reduce bias. This study highlights the critical need to understand T2DM-related dementia in this high-risk population and calls for improved methodologies to identify risk factors and develop targeted interventions.

CONCLUSIONS

This pioneering study demonstrates a significant association between delirium and increased dementia risk in elderly T2DM patients, with a dose-response relationship showing higher risk with multiple episodes. Rigorous methodology, including extensive follow-up, confounder adjustments, and sensitivity analyses, supports the robustness of these findings. Addressing delirium in T2DM patients is critical for preventing diabetes-related dementia and highlights the need for targeted interventions to reduce the growing dementia burden in this population.

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