Journal of Neurology (2019) 266:2233–2243
https://doi.org/10.1007/s00415-019-09405-x

ORIGINAL COMMUNICATION

Type II diabetes mellitus and the incidence of amyotrophic lateral sclerosis

Ching-Piao Tsai[1,2] · Johnny Kuang-Wu Lee[3] · Charles Tzu-Chi Lee[4]

Received: 17 January 2019 / Revised: 23 May 2019 / Accepted: 27 May 2019 / Published online: 31 May 2019

Abstract

Objective The aim of this study was to investigate the relationship between type II diabetes mellitus (T2DM) and ALS incidence using the National Health Insurance Research Database and Serious Disabling Disease database of Taiwan.

Methods This was a population-based cohort study. The index date was the date of the first T2DM diagnosis + 365 days. We included T2DM patients diagnosis between 2000 and 2013 ($n = 2{,}135{,}427$). These patients were matched by sex, age, urbanization, and insurance premium at a ratio of 1:1 to include patients without diabetes mellitus. Competing risk-adjusted Cox regression analysis was performed to investigate the association between T2DM and the incidence of ALS.

Results In the patients not stratified by age, T2DM was not associated with the incidence of ALS after controlling for confounding factors. The interaction test of age subgroup (< 55 and ≥ 55 years) and T2DM on ALS risk was significance ($p < 0.001$). Subgroup analysis showed that T2DM was negatively associated with ALS in patients whose age at the first T2DM diagnosis was ≥ 55 years. Among T2DM patients, T2DM combined with hypertension was negatively associated with ALS among patients whose age at the first T2DM diagnosis was ≥ 55 years. Among T2DM patients, T2DM combined with hyperlipidemia was positively associated with ALS among patients whose age at the first T2DM diagnosis was < 55 years.

Conclusions The late-onset of T2DM may exert negative association with ALS, especially when combined with hypertension. The early-onset of T2DM may exert positive association with ALS, especially when combined with hyperlipidemia.

Keywords Amyotrophic lateral sclerosis · National Health Insurance Database · Serious Disabling Disease Database · Diabetes mellitus · Cohort study

Introduction

Amyotrophic lateral sclerosis (ALS) is known as fatal neurodegenerative disease, due to the degeneration of upper (corticospinal) and lower (spinal and bulbar) motor neurons, which leads to muscle atrophy and eventual paralysis. The mortality rate exceeds 50% in the 5 years following ALS diagnosis [1]. ALS is one of the most dangerous and least understood diseases with a pathophysiology that is still largely unknown [2].

Recent clinical studies suggest that dyslipidemia [3, 4], high body mass index [5, 6], and type 2 diabetes mellitus [5, 7] are associated with better clinical outcomes in ALS. Moreover, ALS patients have a significantly lower incidence of cardiovascular disease, supporting the idea that an unfavorable metabolic profile may be beneficial in ALS [8].

Epidemiology studies have reported an association of some diseases with the pathogenesis of ALS: researchers have reported negative associations with diabetes mellitus (DM) [5, 7, 9–11] and alcohol use disorders [7] and positive associations with psychiatric disorders, [12] vascular diseases [13–15], cancer [16, 17], and autoimmune diseases [18]. By contrast, other studies have found no association of DM [19, 20] and cancer [21] with ALS. Elucidating

Dr. Ching-Piao Tsai and Dr. Johnny Kuang-Wu Lee contributed equally in this study.

✉ Charles Tzu-Chi Lee
Lee@ntnu.edu.tw

1 Department of Biotechnology, Asia University, Taichung, Taiwan

2 Beito Health Management Hospital, Taipei, Taiwan

3 General Education Center, University of Taipei, Taipei, Taiwan

4 Department of Health Promotion and Health Education, National Taiwan Normal University, 162, He-ping East Road, Section 1, Taipei 106, Taiwan

the association between diseases prior to the onset of ALS may lend support to the theory that specific subpopulations exhibit relatively high or low risks of developing ALS and may provide new insights into shared pathogenic mechanisms. We used a nationwide database to investigate the association between type II diabetes mellitus (T2DM) and the incidence of ALS.

Methods

Ethics statement

The present study was approved by the Institutional Review Board (IRB) of National Taiwan Normal University (Protocol No: 201603HM004). Written consent from study patients was not required because data were collected from the National Health Insurance Research Database (NHIRD), which comprises encrypted secondary data released for research purposes. The IRB issued a formal written waiver for the requirement for consent.

Data sources

We conducted this retrospective cohort study using information from the NHIRD [22]. Information regarding outpatient care, hospital inpatient care, ambulatory care, dental services, and prior medical conditions was provided by the National Health Research Institute. The National Health Insurance (NHI) program in Taiwan is a single-payer insurance system operated by the government. This system was established in 1995 to support health nationwide and prevent social problems caused by poverty and disease. In 1997, approximately 20.0 million residents were enrolled in the NHI, with a coverage rate of 94%. In 2003, 21.9 million residents were enrolled in the NHI, with a coverage rate of 96%. The Bureau of NHI (BNHI) has contracted with 17,022 medical institutions, constituting 93.8% of medical institutions nationwide. By the end of 2005, approximately 22.7 million residents were enrolled in Taiwan's NHI program, with a coverage rate of 98%. By December 2010, 23.1 million people were enrolled nationwide, with a coverage rate of 99.6%. The Bureau of the NHI requires registration of all cases of severely disabling diseases (SDDs), such as chronic renal failure, myasthenia gravis, cancer, and ALS for SDD certification.

Study design and population

This was a population-based cohort study. For the consideration of potential induction periods for the development of ALS following the diagnosis of diabetes, the index date was set as the date of the first T2DM diagnosis + 365 days. This study was conducted using the NHIRD and SDD database of Taiwan. We identified patients who had received and any inpatient diagnosis of T2DM (based on the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 250.x0 or 250.x2) or at least three outpatient diagnoses of T2DM within 1 year. The validation of this definition of diabetes showed a sensitivity of 96.9% and a positive predictive value of 93.9% in a previous study based on hypoglycemic agents medical claims of patients with diabetes who were enrolled from the NHIRD [23]. In the present study, patients with T2DM who had not received T2DM diagnosis between 1997 and 1999 but who had received a diagnosis after 2000 were considered as new T2DM-exposed patients. Patients with ALS were identified according to the ICD-9-CM code 335.20. The diagnosis of ALS was based on the decision of the in-charge clinical neurologist, and the medical records of patients were sent to the NHI Bureau. Another group of neurologists of the NHI Bureau verified the medical records of ALS diagnosis to confirm the diagnosis. Only patients with ALS who had SDD certification were included. Patients with SDD certificates are eligible for exemption from insurance premiums and copayments. SDD certification approval is strictly regulated by the Ministry of Health and Welfare, Executive Yuan, Taiwan. In this study, all patients with ALS were verified by linking their encrypted identification numbers with SDD certificates.

We included patients who had received new T2DM diagnosis between 2000 and 2013 ($n = 2{,}135{,}427$). Patients with T2DM were matched by sex, age, urbanization, and insurance premium at a ratio of 1:1 to identify non-DM patients ($n = 2{,}135{,}427$). Total population which removed individual with any ICD-9 code as 250.XX served as non-DM (unexposed) patients. Unexposed patients with birthdays as close as possible to those of their exposed patient's equivalents were included (Fig. 1). The index date of T2DM patients was assigned to their matched non-DM patients and then the age of unexposed patients can be calculated. The variable residence was categorized as rural or urban. Insurance premium was a proxy indicator of economic status and was classified according to four categories: fixed premium and dependent, less than New Taiwan Dollar (NTD) 20,000 monthly, NTD 20,000–39,999 monthly, and NTD 40,000 or more monthly (1 USD = 32.1 NTD in 2008). The fixed premium group comprised people who received social welfare support and included veterans and people with low incomes. The dependent insurance premium group comprised of people with family members who did not have jobs or incomes.

Statistical analysis

The Chi square test or Student's t test was used to examine differences in demographic characteristics between patients

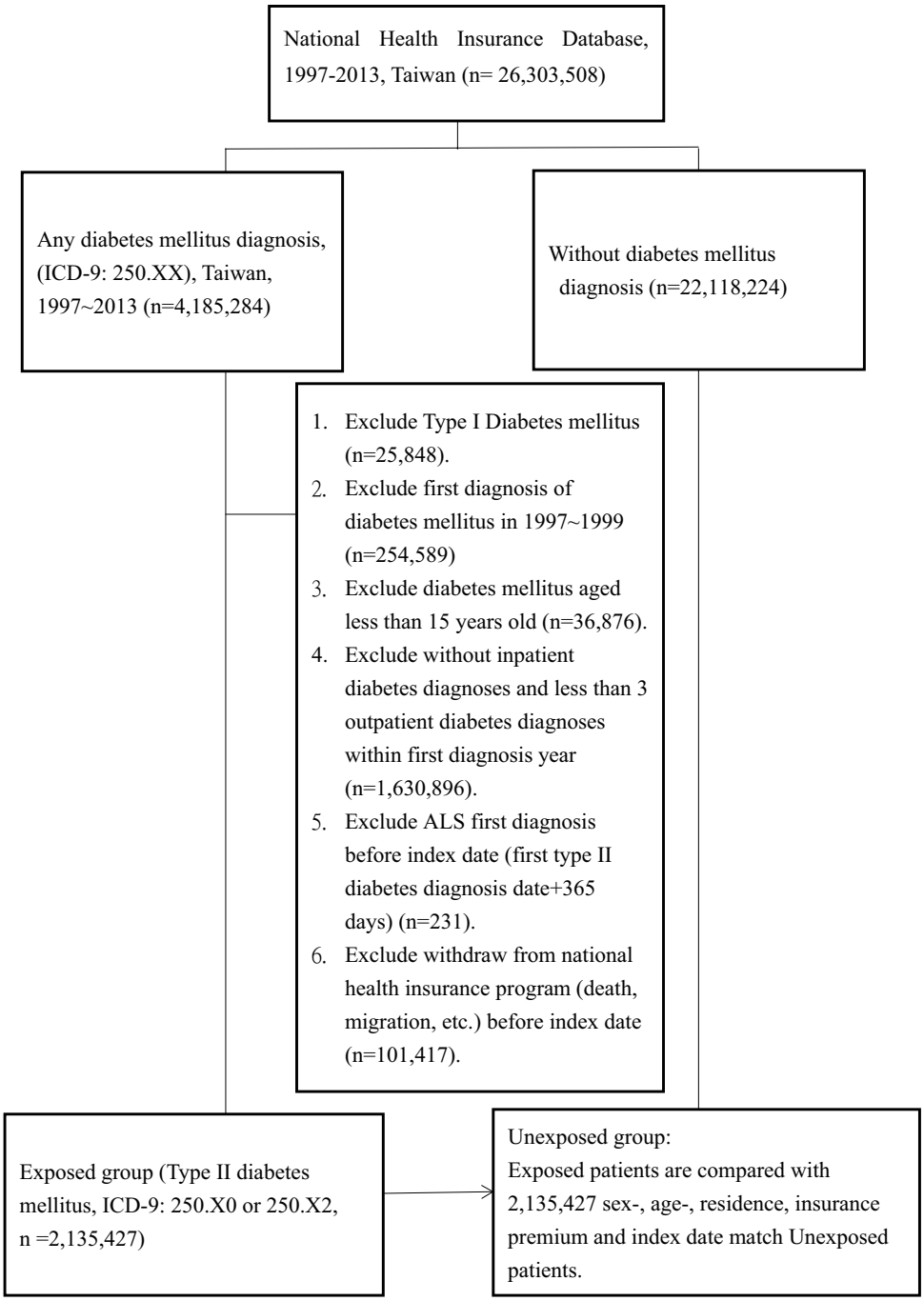

Fig. 1 Flowchart of data collection in this study

who had received a new diagnosis of T2DM and their matched non-DM patients.

Multivariate analysis was performed using competing risk-adjusted Cox regression to evaluate the association between T2DM and the risk of ALS. The time function was calculated as the number of years from the index date to the date of ALS first diagnosis date, death, exit from the NHI program, or December 31, 2014 (the end of follow-up). Competing risk-adjusted hazard ratios (HRs) and 95% confidence interval (CIs) for time-to-ALS incidence were calculated. Since mortality considerably differed between the T2DM and non-DM cohorts, death was considered to be a competing event in our analysis.

The model was tested first with all sample patients. According to our previous study, the mean age at diagnosis of patients with ALS in Taiwan was 56.6 (SD = 13.2) years [1]. After the preliminary model and interaction testing, patients were divided into subgroups according to their T2DM diagnosis age (< 55 and ≥ 55 years) and then analyzed. Finally, among T2DM patients, we examined the

association of T2DM combined with hypertension (HT) and/or hyperlipidemia (HL) with ALS. Hypertension was defined as ICD-9 code as 401.XX and hyperlipidemia was defined as ICD-9 code as 272.XX. Both high LDL cholesterol and high triglycerides included as HL in this study. The validation of HT and HL was considered as more than 1-year duration and at least two outpatient visits or any inpatient diagnosis. In the T2DM cohort, patients were divided into only T2DM, T2DM + HT, T2DM + HL, and T2DM + HT + HL subgroups for further analysis.

To reveal the possible association between medications on ALS, anti-diabetic, anti-hypertensive and anti-lipid were also included in the analysis. The defined daily dose (DDD) recommended by the WHO is a unit for assessing the standard dose of a drug, that is the dose for a 70 (kgw) adult in a day as called one DDD. For example, one DDD for insulin is 40 units parenteral and metformin (an oral anti-diabetic drug) is 2 g. Cumulative DDD (cDDD), which indicates the exposed duration of drug use, was estimated as the sum of dispensed DDD of drug and compared to the risk of ALS. Annual average drug use cDDD during the follow-up period was classified into one of three categories: 0, 1 to the median, and > median. The cutoff point for median was calculated in our study patients by each kind of medication.

Segment analyses during the first 3 years, between 3 and 6 years, more than 6 years after index date were also performed, respectively. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were two-sided, and a p value of < 0.05 was considered statistically significant.

Results

Sample characteristics

The demographic and clinical characteristics of the patients are summarized in Table 1. Due to the exact matching design employed, the age, sex, residence, and insurance premium distributions of the T2DM and non-DM cohorts were equivalent. The mean age of the patients in the T2DM cohort was 57.41 ± 13.33 years, identical to the mean age of the patients in the non-DM cohort. Of the patients in the T2DM cohort, 48% were men; 52% were women, and 78% lived in cities. Furthermore, nearly one-third of the T2DM patients were patients receiving social support or who were a dependent member of a family. Of the patients in the T2DM cohort, 195 people developed ALS compare to 210 for non-DM cohort ($p = 0.456$). The crude mortality rate was 22.65% of T2DM group higher than 13.32% of non-DM group ($p < 0.001$). More detail descriptive statistics for age at T2DM first diagnosis, duration and follow-up time in this study are shown in Table 2. Among T2DM group, the time interval between hypertension and hyperlipidemia to T2DM first diagnosis date was 3.76 ± 3.60 and 3.27 ± 3.50 years, respectively. The ALS incidence of T2DM group was 1.22 (per 100,000 person-years) comparing to 1.23 (per 100,000 person-years) of non-DM group.

Multivariate competing risk-adjusted Cox regression analysis to reveal the association between T2DM and ALS incidence

When the study patients were not stratified by T2DM diagnosis age, T2DM was not found to be associated with the incidence of ALS (HR = 0.87, 95% CI = 0.70–1.07, $p = 0.190$) after controlling for sex, age at the first T2DM diagnosis, urbanization, insurance premium, hospital admission days, outpatient visits, HT, HL, stroke, heart failure, depression, bipolar disorder, chronic kidney disease, cancer, and mortality (Table 3 and Fig. 2).

The interaction test of age subgroup (< 55 and ≥ 55 years) and T2DM on ALS risk was significant ($p < 0.001$). The results of the subgroup analysis are presented in Table 4. In the subgroups categorized according to age at the first T2DM diagnosis, T2DM was found to be negatively associated with ALS among the patients whose age at the first T2DM diagnosis was ≥ 55 years (HR = 0.72, 95% CI = 0.55–0.95, $p = 0.019$). We have no evidence to show the association between T2DM and ALS in the subgroup of the patients whose age at the first T2DM diagnosis was < 55 years (HR = 1.24, 95% CI = 0.88–1.75, $p = 0.223$).

Compared with the only T2DM, T2DM combined HT was negatively associated with ALS in the patients whose age at the first T2DM diagnosis was ≥ 55 years (HR = 0.54, 95% CI = 0.33–0.90, $p = 0.019$). Compared with the only T2DM, T2DM combined HL was positively associated with ALS in the patients whose age at the first T2DM diagnosis was < 55 years (HR = 1.79, 95% CI = 1.02–3.12, $p = 0.041$).

Compared without DM, HT and HL (presented as DM-, HT-, HL- in Table 4), only HT (presented as DM-, HT+, HL- in Table 4) was positively associated with ALS of age ≥ 55 years (HR = 2.59, 95% CI = 1.39–4.84, $p = 0.003$); T2DM combined HT was also negatively associated with ALS (HR = 0.48, 95% CI = 0.30–0.78, $p = 0.003$). Compared without DM, HT and HL, T2DM combined HL was also positively associated with ALS of age < 55 years (HR = 1.94, 95% CI = 1.13–3.32, $p = 0.016$).

Since rare ALS incidences, a segment analysis for all of study patients in this study during the first 3 years after index date was unavailable by Cox regression analysis. Between 3 and 6 years after index date, T2DM was not significantly associated with ALS (HR = 0.85, 95% CI = 0.58–1.23, $p = 0.375$). More than 6 years after index date, T2DM was significantly associated with ALS (HR = 0.68, 95% CI = 0.46–0.99, $p = 0.046$).

Table 1 Characteristic of the subject in this study

Characteristic	T2DM (%)	Non-DM (%)	*p* value
Sex			
Female	1,112,634 (52.1)	1,112,634 (52.1)	> 0.99
Male	1,022,793 (47.9)	1,022,793 (47.9)	
T2DM diagnosis age (year)			
15–44	372,314 (17.44)	372,314 (17.44)	> 0.99
45–54	558,242 (26.14)	558,242 (26.14)	
55–64	562,858 (26.36)	562,858 (26.36)	
≥ 65	642,013 (30.06)	642,013 (30.06)	
Residence			
Rural	464,331 (21.74)	464,331 (21.74)	> 0.99
Urban	1,671,096 (78.26)	1,671,096 (78.26)	
Insurance premium			
Fixed premium and dependent	154,302 (7.23)	154,302 (7.23)	> 0.99
Less than NTD 20,000	618,217 (28.95)	618,217 (28.95)	
NTD 20,000 ~ 39,999	990,088 (46.36)	990,088 (46.36)	
NTD 40,000 or more	372,820 (17.46)	372,820 (17.46)	
Hospital admission days (day)			
0	1,918,001 (89.82)	2,007,565 (94.01)	< 0.001
1–3	57,781 (2.71)	40,715 (1.91)	
≥ 4	159,645 (7.48)	87,147 (4.08)	
Outpatient visits (visit)			
0–10	970,814 (45.46)	1,313,208 (61.5)	< 0.001
11–20	445,588 (20.87)	379,461 (17.77)	
21–30	299,125 (14.01)	209,653 (9.82)	
≥ 31	419,900 (19.66)	233,105 (10.92)	
Hypertension			
No	1,225,793 (57.4)	1,761,489 (82.49)	< 0.001
Yes	909,634 (42.6)	373,938 (17.51)	
Hyperlipidemia			
No	1,449,821 (67.89)	1,936,372 (90.68)	< 0.001
Yes	685,606 (32.11)	199,055 (9.32)	
Stroke			
No	1,961,900 (91.87)	2,054,475 (96.21)	< 0.001
Yes	173,527 (8.13)	80,952 (3.79)	
Heart failure			
No	2,075,394 (97.19)	2,112,253 (98.91)	< 0.001
Yes	60,033 (2.81)	23,174 (1.09)	
Depression			
No	2,059,467 (96.44)	2,084,968 (97.64)	< 0.001
Yes	75,960 (3.56)	50,459 (2.36)	
Bipolar			
No	2,124,798 (99.5)	2,130,216 (99.76)	< 0.001
Yes	10,629 (0.50)	5211 (0.24)	
Chronic kidney disease			
No	2,119,170 (99.24)	2,127,196 (99.61)	< 0.001
Yes	16,257 (0.76)	8231 (0.39)	
Cancer			
No	2,075,927 (97.21)	2,089,937 (97.87)	< 0.001
Yes	59,500 (2.79)	45,490 (2.13)	
Amyotrophic lateral sclerosis (ALS)			
No	2,135,232 (99.99)	2,135,217 (99.99)	0.456

Table 1 (continued)

Characteristic	T2DM (%)	Non-DM (%)	*p* value
Yes	195 (0.01)	210 (0.01)	
Death			
No	1,651,660 (77.35)	1,851,053 (86.68)	< 0.001
Yes	483,767 (22.65)	284,374 (13.32)	
T2DM, HT, HL			
DM-, HT-, HL-	–	1,671,091 (78.26)	
DM-, HT+, HL-	–	265,281 (12.42)	
DM-, HT-, HL+	–	90,398 (4.23)	
DM-, HT+, HL+	–	108,657 (5.09)	
T2DM+, HT-, HL-	921,513 (43.15)	–	
T2DM+, HT+, HL-	528,308 (24.74)	–	
T2DM+, HT-, HL+	304,280 (14.25)	–	
T2DM+, HT+, HL+	381,326 (17.86)	–	

1 US $ = 32.1 New Taiwan Dollars (NTD) in 2008

T2DM type II diabetes mellitus, *HT* hypertension, *HL* hyperlipidemia

Table 2 Descriptive statistics for age, duration and follow-up time in this study

Variable	*n*	Sum	Mean	SD	Min	Max	Median	Q1	Q3
T2DM diagnosis age (year)									
Total subjects	4,270,854	245,203,433	57.41	13.33	14.54	120.14	57.31	48.44	67.26
Among T2DM group (years)	2,135,427	122,601,716	57.41	13.33	14.54	120.14	57.31	48.44	67.26
Among non-DM group (years)	2,135,427	122,601,716	57.41	13.33	14.54	120.14	57.31	48.44	67.26
Duration (years)									
Hypertension- > T2DM	1,283,572	4,832,369	3.76	3.60	0.00	15.75	2.80	0.48	6.21
Hyperlipidemia- > T2DM	884,661	2,890,405	3.27	3.50	0.00	15.97	2.12	0.01	5.56
Index date- > ALS for total subjects	405	2452	6.05	3.39	1.05	14.73	5.52	3.22	8.45
Index date- > ALS among T2DM group	195	1096	5.62	3.44	1.05	14.73	5.06	2.77	7.61
Index date- > ALS among non-DM group	210	1356	6.46	3.30	1.16	14.54	5.99	3.94	9.11
Follow-up from index date (years)									
Total subjects	4,270,854	32,949,039	7.71	4.51	0.00	14.00	7.73	3.68	12.08
Among T2DM group (years)	2,135,427	15,932,303	7.46	4.47	0.00	14.00	7.35	3.49	11.63
Among non-DM group (years)	2,135,427	17,016,736	7.97	4.55	0.00	14.00	8.16	3.91	12.47

n sample size, *SD* standard deviation, *Min* minimum, *Max* maximum, *Q1* first quartile, *Q3* third quartile, *ALS* amyotrophic lateral sclerosis, *T2DM* type II diabetes mellitus, *Index date* T2DM first diagnosis date + 365 days

Medications with ALS incidence

Results for the associations of anti-diabetic, anti-hypertensive, anti-lipid and ALS incidence were summarized in Table 5. There was no statistical evidence to show the association between insulin or other oral anti-diabetic drugs and ALS incidence. Significant medications associated with ALS incidence, including angiotensin-converting-enzyme inhibitors, statin and other non-statin anti-lipid drugs. But the results did not show a clear dose-dependent relationship between these medications and ALS incidence.

Discussion

In the present population-based cohort study, we investigated the relationship between T2DM and the incidence of ALS. The association of T2DM with the incidence of ALS differed between the subgroups based on age at the first T2DM diagnosis and subgroups based on T2DM combined with HT and/or HL. The late-onset of T2DM may exert a negative association with ALS, especially when combined with HT. The early-onset of T2DM may exert positive association with ALS, especially when combined with HL. Our findings support established hypotheses regarding the association of

Table 3 Association of type II diabetes mellitus and amyotrophic lateral sclerosis (ALS), Taiwan, 2000–2013, $n = 4{,}473{,}814$

Variable	Category	No of ALS cases		Unadjusted analysis		Adjusted analysis	
		T2DM	Non-DM	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Type II diabetes mellitus	No			1.00		1.00	
	Yes			0.93 (0.77–1.13)	0.473	0.87 (0.70–1.07)	0.190
Sex	Female	126	121	1.00		1.00	
	Male	69	89	1.73 (1.29–2.32)	< 0.001	1.56 (1.27–1.91)	< 0.001
Type II diabetes mellitus diagnosis age (year)	15–54	83	67	1.00		1.00	
	55–64	71	84	1.39 (1.01–1.90)	0.045	1.43 (1.12–1.81)	0.004
	≥ 65	41	59	0.66 (0.45–0.96)	0.028	0.57 (0.42–0.76)	< 0.001
Insurance premium (NTD[1])	Fixed premium and dependent	52	60	1.00		1.00	
	< 20,000	59	62	0.33 (0.23–0.48)	< 0.001	0.25 (0.18–0.33)	< 0.001
	20,000–39,999	56	65	0.20 (0.14–0.30)	< 0.001	0.15 (0.11–0.20)	< 0.001
	≥ 400,000	28	23	0.29 (0.18–0.46)	< 0.001	0.17 (0.12–0.25)	< 0.001
Residence	Rural	34	57	1.00		1.00	
	Urban	161	153	1.39 (0.96–2.01)	0.082	0.89 (0.70–1.13)	0.335
Hospital admission days (day)	0	182	204	1.00		1.00	
	1–3	5	1	1.01 (0.42–2.45)	0.985	0.63 (0.28–1.41)	0.258
	≥ 4	8	5	0.57 (0.28–1.16)	0.121	0.49 (0.27–0.88)	0.017
Outpatient visits (visit)	0–10	99	128	1.00		1.00	
	11–20	39	34	1.07 (0.74–1.56)	0.712	1.48 (1.12–1.96)	0.006
	21–30	20	24	0.84 (0.52–1.35)	0.464	1.60 (1.12–2.27)	0.009
	≥ 31	37	24	1.12 (0.77–1.63)	0.549	1.95 (1.42–2.69)	< 0.001
Hypertension	No	131	177	1.00		1.00	
	Yes	65	32	0.77 (0.57–1.04)	0.086	0.83 (0.64–1.07)	0.157
Hyperlipidemia	No	131	192	1.00		1.00	
	Yes	64	18	1.29 (0.95–1.75)	0.097	1.48 (1.11–1.96)	0.007
Stroke	No	183	198	1.00		1.00	
	Yes	12	12	0.68 (0.36–1.28)	0.236	0.95 (0.59–1.53)	0.826
Heart failure	No	192	205	1.00		1.00	
	Yes	3	5	0.19 (0.03–1.35)	0.097	0.60 (0.22–1.64)	0.322
Depression	No	187	207	1.00		1.00	
	Yes	8	3	1.28 (0.60–2.72)	0.52	1.33 (0.74–2.37)	0.34
Bipolar	No	186	203	1.00		1.00	
	Yes	9	7	1.33 (0.19–9.48)	0.773	0.73 (0.10–5.11)	0.751
Chronic kidney disease	No	192	208	1.000		1.00	
	Yes	3	2	0.64 (0.09–4.56)	0.658	0.62 (0.20–3.89)	0.723
Cancer	No	191	204	1.00		1.00	
	Yes	4	6	0.43 (0.11–1.73)	0.235	0.72 (0.32–1.65)	0.437

ALS with prior T2DM in Western countries and provide a more comprehensive explanation for the effect of T2DM combined HT and/or HL on ALS.

A Danish nationwide case–control study indicated that diabetes, but not obesity, was associated with a decreased risk of ALS. The association of ALS with diabetes was affected by both aged at ALS diagnosis and age at diabetes diagnosis, with older age at the diagnosis of either disease associated with a lower risk of ALS [10]. A population-based cohort study conducted in Italy also revealed a protective effect of diabetes against ALS [9]. However, another population-based cohort study performed by Sun et al. in Taiwan showed a positive association between diabetes and ALS [20]. The results of the current study conducted in Taiwan are consistent with those reported by previous studies performed in Western countries. The difference in the results of this study and those reported by Sun et al. [20] may be due to the validation of ALS and the coverage of the population;

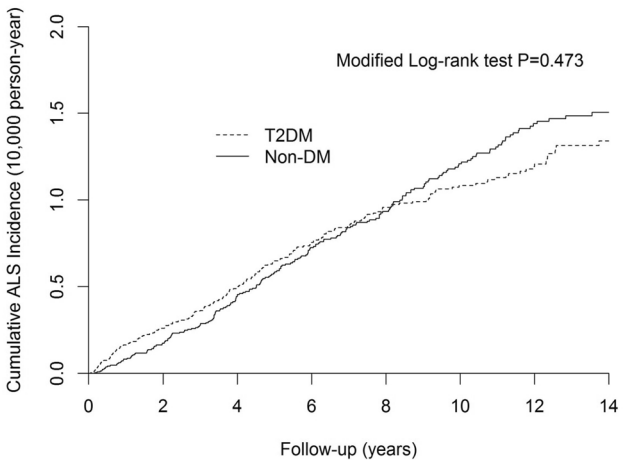

Fig. 2 Type II diabetes mellitus (T2DM) and incidence of ALS after controlling for mortality in Taiwan ($n = 4{,}270{,}854$)

the incidence of ALS was higher in the study conducted by Sun et al. [20] than in our study. All the patients with ALS enrolled in our study were validated using the SDD database to limit false positives, and patients (including exposed and unexposed patients) from a nationwide database of Taiwan's population were included in the analysis.

We found negative association with ALS of T2DM if the T2DM diagnosis is after 55 years and not before. This finding is consistent with those reported by previous studies performed in Western countries [10]. At the meanwhile, we did not find a significant association between anti-diabetic drugs and ALS incidence. The underlying pathophysiological mechanisms of ALS are likely multifactorial with defective energy metabolism and homeostasis likely playing an important role in pathogenesis [24, 25]. The early-onset of T2DM may include more proportion of genetic reason than late-onset patients which include more proportion of environment or lifestyle reason. The relation of genetic and

Table 4 Association of type II diabetes mellitus (T2DM) and amyotrophic lateral sclerosis (ALS), Taiwan, 2000–2013, stratifying by age group and diabetes

Subgroup	Category	Hazard ratio* (95% CI)	*p* value
Total	Non-DM	1.00	
	T2DM	0.87 (0.70–1.07)	0.190
Age ≥ 55 years	Non-DM	1.00	
	T2DM	0.72 (0.55–0.95)	0.019
Age < 55 years	Non-DM	1.00	
	T2DM	1.24 (0.88–1.75)	0.223
Among T2DM, age ≥ 55 years	T2DM+, HT-, HL-	1.00	
	T2DM+, HT+, HL-	0.54 (0.33–0.90)	0.019
	T2DM+, HT-, HL+	1.02 (0.55–1.88)	0.957
	T2DM+, HT+, HL+	1.14 (0.64–2.00)	0.658
Among T2DM, age < 55 years	T2DM+, HT-, HL-	1.00	
	T2DM+, HT+, HL-	1.17 (0.65–2.13)	0.599
	T2DM+, HT-, HL+	1.79 (1.02–3.12)	0.041
	T2DM+, HT+, HL+	0.97 (0.41–2.28)	0.936
Age ≥ 55 years	DM-, HT-, HL-	1.00	
	DM-, HT+, HL-	1.26 (0.79–2.01)	0.334
	DM-, HT-, HL+	2.59 (1.39–4.84)	0.003
	DM-, HT+, HL+	0.67 (0.24–1.86)	0.445
	T2DM+, HT-, HL-	0.89 (0.64–1.24)	0.495
	T2DM+, HT+, HL-	0.48 (0.30–0.78)	0.003
	T2DM+, HT-, HL+	0.95 (0.54–1.69)	0.868
	T2DM+, HT+, HL+	1.08 (0.66–1.78)	0.761
Age < 55 years	DM-, HT-, HL-	1.00	
	DM-, HT+, HL-	1.14 (0.40–3.28)	0.801
	DM-, HT-, HL+	1.13 (0.28–4.66)	0.862
	DM-, HT+, HL+	NA	NA
	T2DM+, HT-, HL-	1.13 (0.75–1.69)	0.563
	T2DM+, HT+, HL-	1.25 (0.70–2.23)	0.459
	T2DM+, HT-, HL+	1.94 (1.13–3.32)	0.016
	T2DM+, HT+, HL+	0.97 (0.42–2.28)	0.952

HT hypertension, *HL* hyperlipidemia, *NA* non-available due to small outcomes *By controlling sex, T2DM first diagnosis age, urbanization, insurance premium, hospital admission days, outpatient visits, hypertension, hyperlipidemia, stroke, heart failure, depression, bipolar, chronic kidney disease, cancer and mortality

Table 5 Association of anti-diabetic, anti-hypertensive, anti-lipid and amyotrophic lateral sclerosis (ALS) in the study patients ($n = 4{,}270{,}854$), Taiwan, 2000–2013

Variable	Category	Hazard ratio[a] (95% CI)	*p* value
Insulin (cDDD)	0	1.00	
	1–312	0.62 (0.21–1.80)	0.378
	> 312	1.23 (0.38–4.00)	0.734
Oral anti-diabetic drugs (cDDD)	0	1.00	
	1–343	0.92 (0.33–2.59)	0.878
	> 343	0.98 (0.32–3.00)	0.967
ACEIs (cDDD)	0	1.00	
	1–23	0.61 (0.41–0.92)	0.019
	> 23	0.77 (0.53–1.10)	0.152
Other anti-hypertensive drugs (cDDD)	0	1.00	
	1–106	1.60 (0.88–2.89)	0.123
	> 106	1.45 (0.77–2.74)	0.250
Statin (cDDD)	0	1.00	
	1–38	0.58 (0.39–0.88)	0.010
	> 38	1.04 (0.72–1.50)	0.833
Other anti-lipid drugs (cDDD)	0	1.00	
	1–19	0.52 (0.31–0.87)	0.013
	> 19	1.16 (0.80–1.71)	0.434

cDDD annual average cumulative defined daily dose during follow-up period, *ACEIs* angiotensin-converting enzyme inhibitors

[a]By controlling sex, type II diabetes mellitus first diagnosis age, urbanization, insurance premium, hospital admission days, outpatient visits, stroke, heart failure, depression, bipolar, chronic kidney disease, cancer, mortality and other drugs in this table

environment may explain the different effect of T2DM on ALS.

When controlled for confounders, antecedent hypertension (high blood pressure), hyperlipidemia (high cholesterol), arthritis, COPD, thyroid disease, and non-ALS neurological disease are found to be statistically associated with a delayed ALS onset age, whereas antecedent obesity [body mass index (BMI) > 30] was correlated to earlier ALS onset age [3]. Diabetes (OR = 0.47); hypertension (OR = 0.56); obesity (OR = 0.6); hyperlipidemia or hypercholesterolemia were also found negatively associated in another case–control study [26]. Angiotensin-converting enzyme inhibitors (ACEIs) are widely used to treat HT. ACEIs may act as a promising factor for future developments in medical treatment for neurological disorders beyond cardiovascular actions [27]. In our previous study, we found that ACEIs exhibited a dose-dependent inverse association with ALS [28]. This cohort study revealed that HT reduced the risk of ALS in the patients with T2DM after 55 years of T2DM diagnosis age, but we did not observe a significant association among patients aged 15–54 years. One possible explanation of this discrepancy may be the longer duration of ACEIs use in older people compared to the younger age group.

A one-unit increase in the low-density lipoprotein cholesterol level (LDL-C; HR = 1.14, 95% CI = 1.02–1.27) was associated with a higher incidence of ALS [29]. A high glucose level (≥ 6.11 mmol/L) was associated with a lower incidence of ALS (HR = 0.62; 95% CI = 0.42–0.93), whereas a high ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C) (≥ 3.50; HR = 1.50, 95% CI = 1.15–1.96) was associated with a higher incidence of ALS. During the 10 years before diagnosis, patients with ALS had increasing levels of LDL-C and HDL-C and a gradually decreasing ratio of LDL-C:HDL-C [29]. The predominance of LDL-C was closely related to hypertriglyceridemia and low HDL-C levels [30]. HL is a form of dyslipidemia characterized by abnormally elevated lipid levels. HL is generally combined with hypertriglyceridemia and hypercholesterolemia. In the present study, HL increased the risk of ALS in patients with T2DM.

Strengths and limitations of this study

This population-based study was conducted using data from the NHIRD, which contains claims data of over 23 million people enrolled in the NHI. The coverage rate of the NHI is 99.6%. The major strengths of this study were the inclusion of a nationwide representative sample, cohort analysis, and potential covariates such as social/economic factors, demographic factors, general health status, and mortality.

This study involved some limitations that should be addressed. The coverage percentage was lower at the beginning of the follow-up (93% in 1997) which increases to over

99% at the end of the follow-up (2013). The database did not contain information on certain crucial information, such as the symptoms of ALS. Misclassification may be occurred in the disease diagnosis of DM, ALS and the other diseases derived from ICD-9 codes and not from clinical/epidemiological registers. Smoking and alcohol consumption are other crucial confounding factors that were not addressed in this study because of a lack of related information in the NHIRD.

Acknowledgements Dr. Charles Tzu-Chi Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This study was supported by grants from the Taiwan Motor Neuron Disease Association (TMND). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author contributions CPT: developing the concept and design of the study; interpretation of data; and writing the first draft. JKWL: developing the concept and design of the study; interpretation of data; and writing the first draft. CTCL: acquisition of data; developing the concept and design of the study; analyzing of data; and writing the first draft.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflicts of interest.

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