Mortality and Suicide Related to Major Depressive Disorder Before and After Type 2 Diabetes Mellitus

Chun-Jen Huang, MD, MPH, PhD[a,b]; Yu-Ting Huang, MS[c]; Pai-Cheng Lin, MD, MS[d]; Hui-Min Hsieh, PhD[e,f,g,h,#]; and Yi-Hsin Yang, PhD[i,#,*]

ABSTRACT

Objective: This study investigated differences in suicide and all-cause mortality from *ICD-9-CM* comorbid major depressive disorder (MDD) and type 2 diabetes mellitus (T2DM) depending on which was diagnosed first.

Methods: A longitudinal administrative claims database including 2 million samples and national death registry data from 2000 through 2015 in Taiwan were used. Patients with newly diagnosed T2DM were identified and further classified into 3 groups: (1) MDD before T2DM, (2) T2DM without any diagnosis of MDD (from which matched controls were selected), and (3) MDD after T2DM, based on the sequential occurrence dates between incident T2DM and MDD. Multivariable Cox proportional hazard models were analyzed.

Results: Both the MDD before T2DM and MDD after T2DM groups had significantly higher risks of all-cause mortality (adjusted hazard ratio [AHR] = 1.21; 95% CI, 1.08–1.35 and AHR = 1.55; 95% CI, 1.45–1.66, respectively) and committed suicide (AHR = 5.05; 95% CI, 2.46–10.37and AHR = 14.32; 95% CI, 7.44–27.55, respectively) than their matched controls, while the MDD before T2DM and MDD after T2DM groups exhibited differences in mortality (significant; $P < .0001$) and death by suicide (nonsignificant).

Conclusions: The study findings indicated suicide and mortality rates were higher in both the MDD before and MDD after T2DM groups when compared with matched controls. Public health initiatives are needed to survey and treat comorbid MDD with T2DM. Furthermore, additional studies are needed to clarify the underlying pathophysiology of the association between MDD and T2DM to find better suicide prevention strategies among those high-risk patients who have comorbid T2DM and MDD.

J Clin Psychiatry 2022;83(1):20m13692

To cite: Huang C-J, Huang Y-T, Lin P-C, et al. Mortality and suicide related to major depressive disorder before and after type 2 diabetes mellitus. *J Clin Psychiatry.* 2022;83(1):20m13692.

To share: https://doi.org/10.4088/JCP.20m13692

[a]Department of Psychiatry, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

[b]Department of Psychiatry, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

[c]Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[d]Department of Psychiatry, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

[e]Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan

[f]Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

[g]Department of Community Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

[h]Center for Big Data Research, Kaohsiung Medical University, Kaohsiung, Taiwan

[i]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

[#]Equal contribution.

**Corresponding author:* Yi-Hsin Yang, PhD, National Institute of Cancer Research, National Health Research Institutes, Taiwan, No.367, Sheng-Li Rd, North District, Tainan, 70456 Taiwan (yhyang@nhri.edu.tw). ORCID: 0000-0002-9581-2778.

Diabetes mellitus (DM), a chronic and disabling disease, has become a worldwide epidemic with a prevalence of 8.3%. DM is a major contributor to disability-adjusted life-years (DALYs).[1–3] DM and its complications impose a heavy burden at both the personal and global levels.[2,4] A study[5] estimated that 693 million people worldwide will have developed DM by 2045. DM is not only a health and economic burden but also a social and psychological challenge that can engender chronic depression.[6] Major depressive disorder (MDD) has a 12-month prevalence of 6.7% in the United States[7] and is one of the most prevalent public health concerns worldwide because of its high rate of morbidity, recurrence, and suicide. MDD presents a considerable burden on both individuals and societies.[8,9] Moreover, MDD is expected to become the predominant cause of DALYs worldwide by 2030.[8]

Increasing evidence has indicated a relationship between depression and DM. Studies[10–12] have indicated that the relationship between DM and depression may be bidirectional. A meta-analysis[12] of 13 studies comprising 6,916 participants determined that depression is predictive of DM. That meta-analysis incorporated 7 studies (comprising 6,414 individuals) in which DM was identified as a risk factor for the development of depression.[12] A prospective study[13] demonstrated that MDD predicted the onset of DM after controlling for age, sex, race, socioeconomic status, and body weight. The relative risk of developing type 2 DM (T2DM) after the onset of a depressive disorder is up to 60%.[12] Furthermore, a meta-analysis[14] revealed that patients with T2DM had a 24% increased risk of depression compared with controls without DM.

Depression in DM is associated with low-quality self-care behaviors, suboptimal glycaemic control, reduced quality of life, incident microvascular and macrovascular diseases, and elevated mortality. Meta-analyses[15,16] of population studies have estimated a 60%–70% increase in the rate of all-cause mortality among people with depression. Because patients with MDD generally exhibit poor self-care, lack of medication compliance, and neglect of diet and exercise, patients with MDD

Clinical Points

- Studies have indicated that the relationship between diabetes mellitus and depression may be bidirectional, but little is known about the differences in suicide and all-cause mortality from comorbid major depressive disorder (MDD) and type 2 diabetes mellitus (T2DM) depending on which was diagnosed first.
- Suicide and mortality rates were higher in both the MDD before and MDD after T2DM groups than for those without MDD. Furthermore, patients with MDD before T2DM and those with MDD after T2DM showed significant differences in mortality and nonsignificant differences in suicidal behaviors.

and T2DM may have increased diabetic complications and higher mortality.[17] Furthermore, researchers have suggested that comorbid DM with depression has an additive effect on mortality.[10] A meta-analysis combined the results of 10 studies and reported that mortality of patients with depression and DM was 1.5 times higher than that of patients with DM but not depression.[18]

Suicide is a leading cause of death worldwide, accounting for nearly 1 million deaths each year, and suicide attempts are even more frequent.[19,20] Unipolar depression and hopelessness are among the most commonly cited risk factors for suicidal thoughts and behaviors.[20] Depression is a severe illness, and, if not properly addressed, it can affect normal functioning and may lead to suicide.[6] The prevalence of lifetime suicide attempts in the general US population is approximately 5%.[21–23] Unfortunately, numerous patients with suicidal ideation or suicide attempts never receive a psychiatric evaluation and commit suicide.[23,24] Chronic medical conditions have been associated with an increased risk of suicide attempts and a 2- to 3-fold increase in MDD.[23,25] Studies have demonstrated that patients with DM have a higher risk of suicidal ideation and suicide attempts than patients without DM.[6,26] Patients with DM are likely to experience depressive symptoms during the course of the disease that may induce suicidal ideation or suicide.[6] However, little is known regarding suicide among patients with T2DM and MDD, and no large-scale epidemiologic studies have evaluated the true rates of suicide attempts and committed suicides.

Given this, the present study hypothesized that patients with T2DM and MDD may be separated as MDD before T2DM and MDD after T2DM. Specifically, this study investigated differences in suicide and all-cause mortality from comorbid MDD and T2DM depending on which was diagnosed first. This study used the National Health Insurance (NHI) database of Taiwan to estimate the suicide and all-cause mortality of patients with MDD before and after T2DM diagnosis. To the best of our knowledge, this study is one of few investigating suicide (suicide attempt or committed suicide) among patients with T2DM and MDD and the first to categorize patients with T2DM and MDD into groups with MDD before and after T2DM.

METHODS

Data Sources

Two national population-based databases were used for this study. The first was the longitudinal health and welfare database, a nationally representative random sample of 2 million National Health Insurance beneficiaries in 2000, from which we obtained information on patient disease conditions or comorbidities through *ICD-9-CM* diagnosis codes or procedures. This database has been verified to be representative of the overall population in terms of age, sex, geographic distribution, and health care costs. The second database was the national death registry (data from 2000 through 2015), which provides accurate death dates and cause-of-death information. This database is managed by the Health and Welfare of Taiwan Data Science Centre, Department of Statistics, Ministry of Health and Welfare; we accessed and analyzed this database in 2017 and 2018. To protect privacy, patient identifications are encrypted, and only authorized researchers are permitted to perform data linkage, processing, and statistical analyses within a designed computing area. Using the encrypted personal identifier for each subject, researchers can link several data files to obtain sociodemographic information, longitudinal medical history, and other data. Only statistical results can be removed from the designated area for publication.

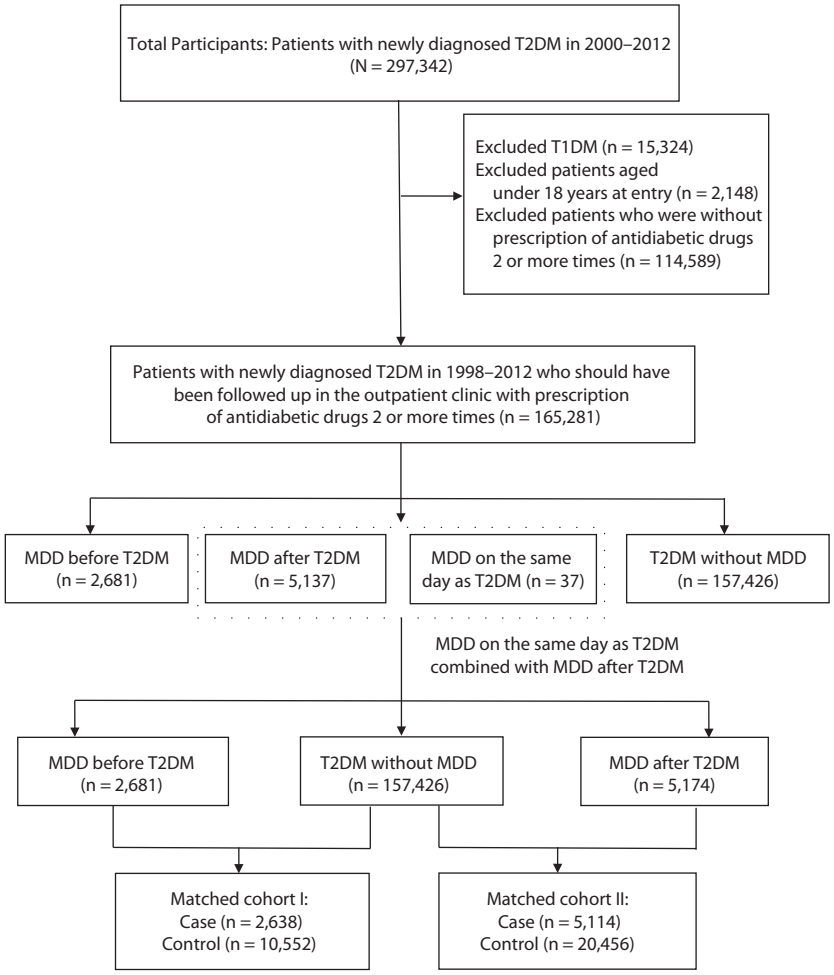
Study Population

The study population comprised patients with newly diagnosed T2DM (*ICD-9-CM* 250.x0 and 250.x2) and with at least 2 prescriptions of antidiabetic drugs within 1 year after the first date of newly diagnosed T2DM in outpatient claims during the patient identification period between 2000 and 2012. The first date of newly diagnosed T2DM was defined as the index date. Patients with or without MDD (*ICD-9-CM* 296.2x and 296.3x) were categorized based on the ambulatory or inpatient claim databases. According to the first MDD diagnosis dates, we further separated participants into 3 groups: (1) MDD diagnosed before T2DM, (2) T2DM without any diagnosis of MDD, and (3) MDD diagnosed after T2DM. The procedure for selecting patients is illustrated in Figure 1. We initially identified 297,342 patients newly diagnosed with T2DM. After applying the inclusion and exclusion criteria, 157,426 patients without MDD, 2,681 patients with MDD diagnosed before T2DM, and 5,174 patients with MDD diagnosed after T2DM were included in the analysis. Matched cohort I included 2,638 patients with MDD diagnosed before T2DM and 10,552 matched control patients. Matched cohort II included 5,114 patients with MDD diagnosed after T2DM and 20,456 matched control patients (Figure 1).

Definitions of Variables

The primary outcomes of this study were the following 3 conditions: all-cause mortality, committed suicide (defined by the Nation Register of Deaths), and suicide attempt (confirmed by *ICD-9-CM* X60–X84, Y87.0, E950–E959

Figure 1. Flowchart of Study Inclusion and Exclusion Criteria



Abbreviations: MDD = major depressive disorder, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.

in the ambulatory claim database). Suicidal behavior was defined as committed suicide or suicide attempt. Each patient was then followed up from the index date for at least 3 years until death event date or study end date on December 31, 2015, whichever came first.

The demographic characteristics included age, sex, income, location, education level, marital status, disease-specific comorbidities, and Charlson Comorbidity Index (CCI) score. Monthly income was classified into 3 categories: NT$0, NT$1–19,200, and > NT$19,200. The exchange rate between New Taiwan Dollar and United States Dollar (is about 1:30 in this study. Location was classified into 4 geographic regions of Taiwan: northern, central, southern, and eastern Taiwan. Education level was classified into 4 categories: primary school (6 years of schooling), secondary school (9 years of schooling), high school (12 years of schooling), and university or above. Marital status was classified into 3 categories: unmarried, married, and divorced or widowed. The CCI was an *ICD-9-CM* coding adaption to identify levels of overall chronic illness severity in each phase by classifying or weighting comorbid conditions. This index has been widely used by health researchers to measure general disease severity and case mix, with low scores representing lowest risk.[27,28] CCI scores were classified as 0, 1–2, and > 2. Other common disease-specific comorbidities associated with MDD and T2DM were included, such as neurologic disease, peripheral vascular disease, cardiovascular disease, renal disease, other endocrine or metabolic disease, ophthalmic disease, and generalized anxiety disorder (GAD).[9] Detailed *ICD-9-CM* codes for these specific comorbidities are listed in Supplementary Table 1.

Statistical Analysis

The distribution of demographic status and comorbidity were compared among the 3 groups (T2DM without MDD, MDD before T2DM, and MDD after T2DM) by using χ^2 tests and analysis of variance (ANOVA). The baseline characteristics were significantly different between the 3 groups, which lead to the concern of imbalance. To address potential selection bias and confounding factors, we used a propensity score matching (PSM) approach with 1-to-4 match to determine adequate comparison groups.[29] We

Table 1. Demographic Status, Comorbidity, and Outcome Compared in All Participants (N = 165,281)[a]

Variable and Class	Total n	T2DM Without MDD Value[b]	MDD Before T2DM Value[b]	MDD After T2DM Value[b]	*P* Value: Comparison Among All 3 Groups	*P* Value: Without MDD vs MDD Before[c]	*P* Value: Without MDD vs MDD After[d]	*P* Value: MDD Before vs MDD After[e]
Overall	165,281	157,426 (95.2)	2,681 (1.6)	5,174 (3.1)				
Age, mean ± SD, y	165,281	58.11 ± 12.9	57.09 ± 13.8	57.99 ± 12.6	.0002			
Sex					< .0001	< .0001	< .0001	1.0000
Male	86,886	83,817 (53.2)	1,058 (39.5)	2,011 (38.9)				
Female	78,395	73,609 (46.8)	1,623 (60.5)	3,163 (61.1)				
Monthly income, NT$[f]					< .0001	.0002	< .0001	< .0001
0	40,600	633 (23.6)	1,479 (28.6)	38,488 (24.4)				
1–19,200	29,940	571 (21.3)	1,047 (20.2)	28,322 (18.0)				
> 19,200	94,741	1,477 (55.1)	2,648 (51.2)	90,616 (57.6)				
Region					< .0001	< .0001	< .0001	.0113
Northern	73,337	69,953 (44.4)	1,198 (44.7)	2,186 (42.2)				
Central	28,893	27,618 (17.5)	394 (14.7)	881 (17.0)				
Southern	54,484	51,684 (32.8)	976 (36.4)	1,824 (35.3)				
Eastern	4,835	4,581 (2.9)	68 (2.5)	186 (3.6)				
Education level					< .0001	< .0001	< .0001	< .0001
Primary school	89,675	85,430 (54.3)	1,225 (45.7)	3,020 (58.4)				
Secondary school	27,605	26,228 (16.7)	521 (19.4)	856 (16.5)				
High school	30,971	29,506 (18.7)	587 (21.9)	878 (17.0)				
University or above	17,030	16,262 (10.3)	348 (13.0)	420 (8.1)				
Marital status					< .0001	< .0001	.0002	< .0001
Unmarried	14,343	13,606 (8.6)	349 (13.0)	388 (7.5)				
Married	124,065	118,346 (75.2)	1,868 (69.7)	3,851 (74.4)				
Divorced/spouse died	26,873	25,474 (16.2)	464 (17.3)	935 (18.1)				
CCI score, mean ± SD	165,281	1.47 ± 2.7	2.42 ± 3.3	1.76 ± 2.9	.0001			
CCI score					< .0001	< .0001	.0511	< .0001
0	68,029	65,491 (41.6)	369 (13.8)	2,169 (41.9)				
1	37,538	35,909 (22.8)	532 (19.8)	1,097 (21.2)				
≥ 2	59,714	56,026 (35.6)	1,780 (66.4)	1,908 (36.9)				
Comorbidity								
Neurologic disease	39,528	36,942 (23.5)	1,288 (48.0)	1,298 (25.1)	< .0001	< .0001	.0205	< .0001
Peripheral vascular disease	13,496	12,625 (8.0)	468 (17.5)	403 (7.8)	< .0001	< .0001	1.0000	< .0001
Cardiovascular disease	85,197	80,573 (51.2)	1,992 (74.3)	2,632 (50.9)	< .0001	< .0001	1.0000	< .0001
Renal disease	49,163	45,991 (29.2)	1,554 (58.0)	1,618 (31.3)	< .0001	< .0001	.0041	< .0001
Endocrine/metabolic disease	43,997	41,438 (26.3)	1,259 (47.0)	1,300 (25.1)	< .0001	< .0001	.1631	< .0001
Ophthalmic disease	38,069	35,798 (22.7)	1,080 (40.3)	1,191 (23.0)	< .0001	< .0001	1.0000	< .0001
GAD	3,194	2,548 (1.6)	436 (16.3)	210 (4.1)	< .0001	< .0001	< .0001	< .0001
Outcome								
All-cause mortality	44,581	42,355 (26.9)	534 (19.9)	1,692 (32.7)	< .0001	< .0001	< .0001	< .0001
Committed suicide	539	451 (0.3)	23 (0.9)	65 (1.3)	< .0001	< .0001	< .0001	.112
Suicide attempt	97	53 (0.0)	13 (0.5)	31 (0.6)	< .0001	< .0001	< .0001	.520
Suicidal behavior	636	504 (0.3)	36 (1.3)	96 (1.9)	< .0001	< .0001	< .0001	.094

[a]Analysis with 1-way ANOVA indicated a statistically significant difference among the groups in age and CCI score; further analysis with Tukey pairwise comparison was as follows: age: MDD after T2DM > MDD before T2DM, T2DM without MDD > MDD before T2DM; CCI score: MDD before T2DM > MDD after T2DM, MDD before T2DM > T2DM without MDD.
[b]Values are shown as n (%) unless otherwise noted.
[c]Bonferroni correction for T2DM without MDD vs MDD before T2DM.
[d]Bonferroni correction for T2DM without MDD vs MDD after T2DM.
[e]Bonferroni correction for MDD before T2DM vs MDD after T2DM.
[f]The exchange rate between NT$ and US dollars is about 1:30 in this study.
Abbreviations: ANOVA = analysis of variance, CCI = Charlson Comorbidity Index, GAD = generalized anxiety disorder, MDD = major depressive disorder, NT$ = New Taiwan dollar, T2DM = type 2 diabetes mellitus.

created propensity scores using logistic regressions with the covariates listed in Table 1. The first cohort (matched cohort I) matched patients diagnosed with MDD before T2DM to patients with T2DM without a diagnosis of MDD, and the second matched cohort (matched cohort II) matched patients diagnosed with MDD after T2DM with patients with T2DM without a diagnosis of MDD. Cumulative incidences of death and suicide outcomes were analyzed and compared using the Kaplan-Meier method and log rank test. Multivariable Cox proportional hazards models were used and adjusted for all covariates listed in the Table 1. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. The proportional hazard assumption was tested. Nonproportionality was detected, which may cause bias when directly interpreting estimations of model results.[30] To deal with nonproportionality, this study, following the approach of Therneau and Grambsch,[31] stratified and subgrouped the models by patient demographic categories, CCI score categories, and individual comorbid covariates so that each variable has its own baseline hazard (results from

Table 2. Results for Adjusted Hazard Ratio Using Multivariable Cox Proportional Hazards Regressions in All Participants (N = 165,281)

	All-Cause Mortality			Committed Suicide			Suicide Attempt			Suicide Behavior		
Variable and Class	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value
Group												
T2DM without MDD	1.00			1.00			1.00			1.00		
MDD before T2DM	1.12	1.03–1.22	.0093	4.01	2.60–6.19	<.0001	14.8	7.71–28.28	<.0001	5.41	3.80–7.69	<.0001
MDD after T2DM	1.01	0.96–1.06	.7361	4.26	3.28–5.53	<.0001	15.4	9.80–24.07	<.0001	5.54	4.44–6.90	<.0001
Age	1.07	1.06–1.07	<.0001	0.99	0.98–0.99	.0015	0.99	0.97–1.00	.1161	0.99	0.98–0.99	.0003
Sex												
Male	1.00			1.00			1.00			1.00		
Female	0.59	0.58–0.60	<.0001	0.33	0.27–0.40	<.0001	1.19	0.76–1.85	.4461	0.41	0.34–0.49	<.0001
CCI score												
0	1.00			1.00			1.00			1.00		
1	0.99	0.96–1.02	.5675	1.04	0.82–1.32	.7386	2.08	1.19–3.64	.0104	1.16	0.93–1.44	.1925
≥2	1.46	1.42–1.50	<.0001	1.22	0.96–1.56	.1039	2.60	1.46–4.63	.0012	1.37	1.10–1.71	.0056
Comorbidities												
Neurologic disease												
No	1.00			1.00			1.00			1.00		
Yes	1.10	1.08–1.13	<.0001	0.92	0.73–1.16	.4849	0.85	0.51–1.43	.5431	0.91	0.74–1.12	.3683
Peripheral vascular disease												
No	1.00			1.00			1.00			1.00		
Yes	1.07	1.03–1.10	.0004	0.88	0.62–1.25	.4838	0.72	0.31–1.69	.4558	0.86	0.62–1.18	.3421
Cardiovascular disease												
No	1.00			1.00			1.00			1.00		
Yes	0.89	0.87–0.91	<.0001	1.19	0.97–1.46	.0886	0.91	0.57–1.44	.6853	1.14	0.95–1.37	.1683
Renal disease												
No	1.00			1.00			1.00			1.00		
Yes	1.08	1.05–1.10	<.0001	1.04	0.84–1.29	.7081	0.81	0.50–1.31	.3877	1.01	0.83–1.22	.9469
Endocrine/metabolic disease												
No	1.00			1.00			1.00			1.00		
Yes	0.66	0.65–0.68	<.0001	0.94	0.75–1.17	.5604	1.04	0.64–1.68	.8863	0.95	0.78–1.16	.6074
Ophthalmic disease												
No	1.00			1.00			1.00			1.00		
Yes	0.84	0.82–0.86	<.0001	1.01	0.80–1.27	.9206	0.50	0.27–0.93	.0293	0.91	0.74–1.13	.4115
GAD												
No	1.00			1.00			1.00			1.00		
Yes	0.73	0.66–0.80	<.0001	1.08	0.59–1.99	.8061	1.43	0.56–3.67	.4562	1.18	0.71–1.96	.5324

Abbreviations: AHR = adjusted hazard ratio, CCI = Charlson Comorbidity Index, GAD = generalized anxiety disorder, MDD = major depressive disorder, T2DM = type 2 diabetes mellitus.

overall group and subgroup cohorts are reported in Table 3). The data linkage, sampling, and statistical analysis were performed using SAS version 9.4 (SAS Institute, Inc; Cary, North Carolina). A *P* value < .05 was considered statistically significant.

Ethics Statement

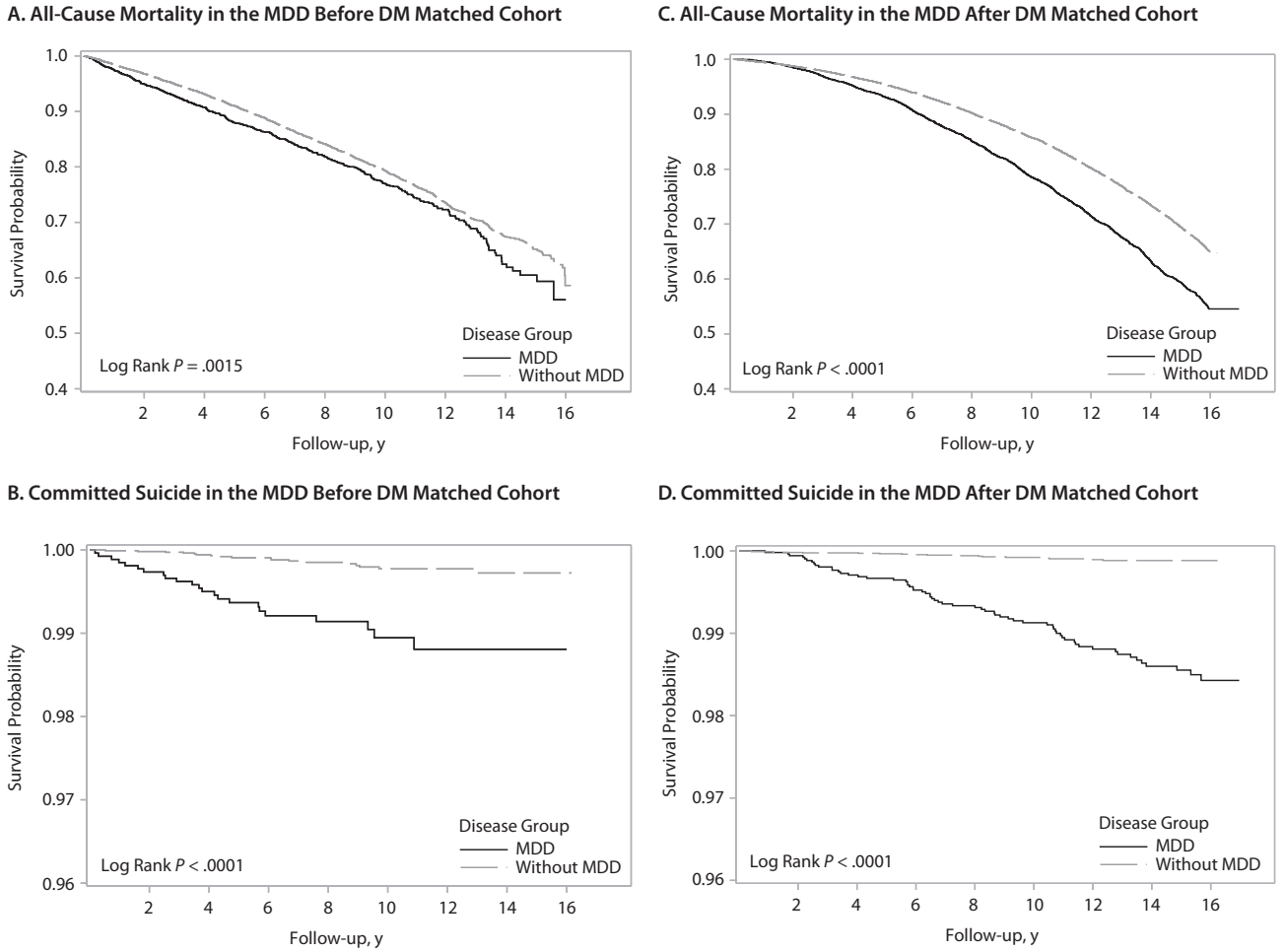
The current study was also approved by the Institutional Review Board of Kaohsiung Medical University: IRB number KMUHIRB-EXEMPT(I)-20180042.

RESULTS

The demographic characteristics and outcomes were compared among the T2DM without MDD group (n = 157,426), MDD before T2DM group (n = 2,681), and MDD after T2DM group (n = 5,174; Table 1). These 3 groups differed significantly in all analysis variables, and we further performed post hoc comparisons by using the Bonferroni correction. The MDD before T2DM and T2DM without MDD groups differed significantly in all demographic characteristics and comorbidities. The MDD after T2DM and T2DM without MDD groups differed significantly in all demographic characteristics except CCI score and certain comorbidities (ie, peripheral vascular disease, cardiovascular disease, endocrine/metabolic disease, and ophthalmic disease). The MDD before T2DM and MDD after T2DM groups differed significantly in all demographic characteristics except sex. The ages of patients in the MDD after T2DM and T2DM without MDD groups were higher than in the MDD before T2DM group. The mean CCI score in the MDD before T2DM group was higher than those in the MDD after T2DM and T2DM without MDD groups. Table 1 also reports the crude rates for all-cause mortality and death from suicides among the 3 groups. From results of the post hoc tests, risks of all-cause mortality among each pair of 3 groups were all significantly different ($P < .001$). As to the risks of committed suicide, suicide attempt, and suicide behavior, the testing results were significant when compared for MDD before or after T2DM with T2DM without MDD ($P < .001$), while no significant differences were found between the MDD before and after T2DM groups.

The associations of the 3 groups with the 4 outcomes were further analyzed using a multivariable Cox proportional hazards regressions, as Table 2 shows. Compared with the T2DM without MDD group, the MDD before T2DM group had significantly higher risks of all-cause mortality (adjusted HR [AHR] = 1.12; 95% CI, 1.03–1.22), committed

Figure 2. Kaplan-Meier Curves for All-Cause Mortality and Committed Suicide in the MDD Before DM and MDD After DM Matched Cohorts



Abbreviations: DM = diabetes mellitus (type 2), MDD = major depressive disorder.

suicide (AHR = 4.01; 95% CI, 2.60–6.19), suicide attempt (AHR = 14.8; 95% CI, 7.71–28.28), and suicidal behavior (AHR = 5.41; 95% CI, 3.80–7.69). Compared with the T2DM without MDD group, the MDD after T2DM group had significantly higher risks of committed suicide (AHR = 4.26; 95% CI, 3.28–5.53), suicide attempt (AHR = 15.4; 95% CI, 9.80–24.07), and suicidal behavior (AHR = 5.54; 95% CI, 4.44–6.90).

The significant differences among the baseline characteristics of the 3 MDD and T2DM groups led to a concern about imbalance. Therefore, we performed propensity score matching. Comparisons of baseline characteristics are reported in Supplementary Tables 2 and 3. Table 3 includes matched cohorts (MDD before T2DM and MDD after T2DM with T2DM without MDD), which were comparable pairs with T2DM without MDD controls in terms of their baseline characteristics, to investigate risks of outcomes of interest separately in MDD before or after T2DM pairs using Cox proportional hazard regressions. All models were adjusted for income, education level, marital status, CCI score, neurologic disease, peripheral vascular disease, cardiovascular disease, renal disease, and GAD.

Because the number of suicide attempts was too small to analyze among matched cohorts separately for MDD before or after T2DM groups, the analysis was performed only for all-cause mortality and committed suicide. Both the MDD before T2DM and MDD after T2DM groups had significantly higher risks of all-cause mortality (MDD before T2DM: AHR = 1.21; 95% CI, 1.08–1.35; MDD after T2DM: AHR = 1.55; 95% CI, 1.45–1.66) and committed suicide (MDD before T2DM AHR = 5.05; 95% CI, 2.46–10.37; MDD after T2DM: AHR = 14.32; 95% CI, 7.44–27.55) than their matched controls. For committed suicide, the AHR of the MDD after T2DM group was slightly higher than that of the MDD before T2DM group, but the confidence intervals overlapped. Figure 2 compares the Kaplan-Meier curves of temporal trends in all-cause mortality and committed suicide in the matched cohorts for MDD before T2DM and MDD after T2DM. Both the MDD before and after T2DM groups had significantly higher risks of all-cause mortality and committed suicide than their corresponding matched control groups.

Results from the subgroup analysis in Table 3 were similar to those of the entire sample analysis. In the

Table 3. Adjusted Hazard Ratio for Analysis Variables in MDD Before T2DM and MDD After T2DM Matched Cohorts[a]

	MDD Before T2DM Matched Cohort (n = 13,190)						MDD After T2DM Matched Cohort (n = 25,570)					
	All-Cause Mortality			Committed Suicide			All-Cause Mortality			Committed Suicide		
Variable and Class	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value	AHR	95% CI	*P* Value
Group												
Without MDD	1.00			1.00			1.00			1.00		
MDD	1.21	1.08–1.35	.0001	5.05	2.46–10.37	<.0001	1.55	1.45–1.66	<.0001	14.32	7.44–27.55	<.0001
Subgroup analysis[b]												
Sex												
Male	1.14	0.97–1.34	.1016	4.11	1.65–10.20	.0023	1.60	1.45–1.77	<.0001	18.72	6.04–58.05	<.0001
Female	1.26	1.08–1.47	.0030	8.51	1.66–43.64	.0102	1.52	1.39–1.66	<.0001	16.02	6.45–39.78	<.0001
Age group, y												
<65	1.21	1.01–1.45	.0352	6.65	2.66–16.64	<.0001	2.06	1.86–2.28	<.0001	26.66	9.09–78.19	<.0001
≥65	1.19	1.04–1.37	.0143	2.98	0.73–12.07	.1272	1.27	1.17–1.39	<.0001	8.77	3.04–25.29	<.0001
Income												
No	1.05	0.82–1.33	.7071				1.45	1.29–1.64	<.0001	15.02	4.31–52.34	<.0001
Yes	1.22	1.06–1.41	.0055	4.85	2.12–11.10	.0002	1.61	1.48–1.75	<.0001	13.79	5.55–34.29	<.0001
Education level												
Primary and Secondary school	1.15	1.01–1.31	.0327	4.10	1.75–9.65	.0012	1.47	1.36–1.58	<.0001	10.43	5.12–21.24	<.0001
Above high school	1.26	0.95–1.68	.1129	9.94	1.07–92.68	.0437	1.83	1.51–2.23	<.0001			
Marital status												
Unmarried	0.76	0.40–1.42	.3832	3.24	0.29–36.23	.3428	2.55	1.64–3.96	<.0001	2.00	0.18–22.06	.5714
Married (included widowed and divorced)	1.14	0.98–1.31	.0816	6.30	2.08–19.07	.0011	1.56	1.44–1.70	<.0001	37.36	10.50–133.00	<.0001
CCI score												
0	1.19	0.80–1.77	.3984				1.62	1.46–1.79	<.0001	9.46	3.08–29.07	<.0001
≥1	1.19	1.06–1.34	.0035	8.53	3.16–23.05	<.0001	1.47	1.34–1.62	<.0001	19.41	7.79–48.39	<.0001
Neurologic disease												
No	1.08	0.89–1.31	.4297	5.15	1.66–15.96	.0046	1.64	1.51–1.77	<.0001	13.47	5.87–30.95	<.0001
Yes	1.27	1.09–1.49	.0023	4.66	1.15–18.86	.0310	1.42	1.20–1.68	<.0001	30.27	3.91–234.11	.0011
Peripheral vascular disease												
No	1.28	1.13–1.46	.0002	4.94	2.28–10.71	<.0001	1.56	1.46–1.67	<0.0001	12.49	6.43–24.25	<.0001
Yes	1.25	0.91–1.72	.1678				1.37	0.92–2.04	.1237			
Cardiovascular disease												
No	1.38	1.03–1.85	.0317	5.46	0.94–31.82	.0589	1.65	1.50–1.82	<.0001	12.98	4.81–35.80	<.0001
Yes	1.17	1.03–1.33	.0132	6.78	2.45–18.77	.0002	1.42	1.28–1.58	<.0001	19.84	5.94–66.29	<.0001
Renal disease												
No	1.28	1.06–1.54	.0108	4.47	1.25–15.97	.0211	1.65	1.53–1.79	<.0001	12.61	5.82–27.32	<.0001
Yes	1.16	0.99–1.36	.0697	5.71	1.43–22.78	.0135	1.19	1.01–1.40	.0370			
Endocrine/metabolic disease												
No	1.19	1.02–1.38	.0286	4.36	1.46–13.00	.0082	1.53	1.42–1.65	<.0001	11.10	5.55–22.19	<.0001
Yes	1.29	1.04–1.59	.0184				1.62	1.34–1.97	<.0001	19.72	2.52–154.55	.0045
Ophthalmic disease												
No	1.22	1.04–1.44	.0151	5.49	1.89–15.94	.0017	1.63	1.51–1.76	<.0001	26.70	9.85–72.37	<.0001
Yes	1.15	0.96–1.37	.1209				1.30	1.10–1.54	.0018	5.70	1.47–22.15	.0119
GAD												
No	1.19	1.06–1.33	.0038	5.13	2.41–10.94	<.0001	1.56	1.46–1.67	<.0001	14.03	7.28–27.05	<.0001
Yes	1.36	0.88–2.11	.1673				1.07	0.54–2.12	.8511			

[a]Since suicide attempt number is too small, the analysis was conducted only for all-cause mortality and committed suicide.
[b]Subgroup analysis for MDD vs without MDD in matched cohort.
Abbreviations: AHR = adjusted hazard ratio, CCI = Charlson Comorbidity Index, GAD = generalized anxiety disorder, MDD = major depressive disorder, T2DM = type 2 diabetes mellitus.

subgroup analysis—for both the MDD before and after T2DM groups, respectively—patients aged younger than 65 years (AHR = 6.65; 95% CI, 2.66–16.64; AHR = 26.66; 95% CI, 9.09–78.19), those with an income (AHR = 4.85; 95% CI, 2.12–11.10; AHR = 13.79; 95% CI, 5.55–34.29), those who were married (AHR = 6.30; 95% CI, 2.08–19.07; AHR = 37.36; 95% CI, 10.50–133.00), those with CCI score ≥ 1 (AHR = 8.53; 95% CI, 3.16–23.05; AHR = 19.41; 95% CI, 7.79–48.39), and those with cardiovascular disease (AHR = 6.78; 95% CI, 2.45–18.77; AHR = 19.84; 95% CI, 5.94–66.29) had significantly higher risks of committing suicide than the matched controls.

DISCUSSION

Suicide

Very few studies have been conducted on suicide in patients with T2DM and MDD, although several psychological autopsy studies have repeatedly reported that depression is the most common mental illness among people who commit suicide.[20] Our findings indicated both the MDD before and MDD after T2DM groups exhibited significantly higher risks of committed suicide, suicide attempt, and suicidal behavior than the T2DM without MDD group. The current findings were consistent with those of previous

studies. For example, Myers et al[23] indicated that, among patients with T2DM, the rate of past suicide attempts was nearly 10%, which is double the rate observed in the general population. The rate of past suicide attempts in patients with concurrent depression and DM is 21.8%. Depression is defined as a mood disorder that causes a persistent feeling of sadness and loss of interest, which can cause emotional and physical problems. Moreover, depression can lead to suicidal feelings and suicide attempts.[32] Many epidemiologic studies have linked non-fatal suicide attempts with the presence of a mood disorder.[33]

All-Cause Mortality

The current study also found that patients with MDD before and after T2DM had significantly higher risks of all-cause mortality than the matched T2DM without MDD patients. After adjustment of the variables, the AHRs revealed that both the MDD before and MDD after T2DM groups had significantly higher risks of all-cause mortality than their matched controls. These findings were also consistent with those of previous studies[18,34–38] which showed that DM with depression results in a higher mortality risk than DM without depression (HRs: 1.25–1.6).

MDD Before T2DM Group vs MDD After T2DM Group

Furthermore, to the best of our knowledge, very few studies have investigated mortality risks in patients with MDD before T2DM and MDD after T2DM. The MDD before T2DM and MDD after T2DM groups significantly differed in all demographic characteristics except sex distribution. Compared with the MDD before T2DM group, MDD after T2DM patients were at similar or only slightly higher risk of committed suicide in all groups and subgroups. These findings demonstrated that the MDD before T2DM and MDD after T2DM groups may be heterogeneous in all-cause mortality. The relationship between DM and MDD could be bidirectional, with one disease increasing the risk of developing the other disease.[39] This finding could help further clarify the causal relationship between MDD and T2DM. Additional studies are required to clarify the underlying pathophysiology of the association between MDD and T2DM.

Demographic Characteristics and Comorbidities

The MDD before T2DM and T2DM without MDD groups significantly differed in terms of all demographic characteristics and all comorbidities. The MDD after T2DM and T2DM without MDD groups significantly differed in all demographic characteristics except CCI index and certain comorbidities (ie, peripheral vascular disease, cardiovascular disease, endocrine/metabolic disease, and ophthalmic disease). The MDD before T2DM and MDD after T2DM groups significantly differed in all demographic characteristics except sex. Studies have demonstrated that patients with T2DM and MDD have more cardiovascular risk factors, more diabetic microvascular complications, and higher incidences of cerebrovascular disease, stroke, and chronic kidney disease.[37,40] The ages of patients in the MDD after T2DM and T2DM without MDD groups were higher than in the MDD before T2DM group. The Pathways Study revealed that minor depression, major depression, and older age were associated with a significant increase in mortality in patients with T2DM.[41] The CCI scores in the MDD before T2DM group were higher than those in the MDD after T2DM group and the T2DM without MDD group. These findings indicated that the MDD before T2DM and MDD after T2DM groups fundamentally differed from the T2DM without MDD group.

Strengths and Limitations

Our study has several strengths. First, to the best of our knowledge, this study was the first to distinguish risks of all-cause mortality and death by suicide among patients with MDD before T2DM, MDD after T2DM, and T2DM only. However, whether the duration between MDD and T2DM (before or after) affects the mortality risks is still unknown. Future study may take further steps to investigate this question. Second, this study was one of the few to investigate suicide among patients with T2DM and MDD. Third, we investigated a high number of samples, which were tracked over 16 years (2000–2015). However, our study also had several limitations that must be considered when interpreting findings. First, the potential reason for the small number of suicide attempts may be that people in Eastern culture may avoid any stigmatization from their medical records. Downcoding or conservative coding may thus occur in the cases of suicide attempts in the health administrative claims data. Given that, we reported only all-cause mortality and committed suicide among 3 groups. Second, several essential variables were not recorded in the administrative claims data, including laboratory data, body weight, lifestyle factors, and physical activity. Third, this study did not discuss treatment types or calculate the accumulated medication dosages, which could be a critical factor in comorbid T2DM and MDD.

CONCLUSION

In conclusion, the study findings indicated suicide and mortality rates were higher in both the MDD before and MDD after T2DM groups when compared with matched controls. Public health initiatives are needed to survey and treat comorbid MDD and T2DM. Furthermore, additional studies are needed to clarify the underlying pathophysiology of the association between MDD and T2DM to find better suicide prevention strategies among those high-risk patients who have comorbid T2DM and MDD.

Submitted: September 15, 2020; accepted August 11, 2021.
Published online: January 11, 2022.
Potential conflicts of interest: None.
Funding/support: This study was supported by a grant from Kaohsiung Medical University Hospital (KMUH108-8T06) and Kaohsiung Medical University (KMU-M108016). This study is based in part on data from the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW) (H106094 and H109076).

Role of the sponsor: The funding agencies had no role in the design, conduct, interpretation, or reporting for this study.

Disclaimer: The interpretation and conclusions contained herein do not represent those of the aforementioned agencies.

Acknowledgments: The authors thank the Center for Medical Informatics and Statistics of Kaohsiung Medical University for providing administrative and funding support. The authors also thank the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, and Center for Big Data Research (KMU-KMU-TC109B08), Kaohsiung Medical University for providing administrative support, including the Kaohsiung Medical University Hospital Research Database (KMUHRD). This manuscript was edited by Wallace Academic Editing.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Akena D, Kadama P, Ashaba S, et al. The association between depression, quality of life, and the health care expenditure of patients with diabetes mellitus in Uganda. *J Affect Disord*. 2015;174:7–12.
2. Lin W-H, Hsu C-H, Chen H-F, et al. Mortality of patients with type 2 diabetes in Taiwan: a 10-year nationwide follow-up study. *Diabetes Res Clin Pract*. 2015;107(1):178–186.
3. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–2223.
4. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med*. 1997;14(suppl 5):S1–S85.
5. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271–281.
6. Sweileh WM. Analysis of global research output on diabetes depression and suicide. *Ann Gen Psychiatry*. 2018;17(1):44.
7. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617–627.
8. Gaynes BN, Jackson WC, Rorie KD. Major depressive disorder in the primary care setting: strategies to achieve remission and recovery. *J Fam Pract*. 2015;64(9):S4–S15.
9. Huang C-J, Hsieh H-M, Tu H-P, et al. Major depressive disorder in patients with type 2 diabetes mellitus: prevalence and clinical characteristics. *J Affect Disord*. 2018;227:141–148.
10. Lee SY, Choi SH. Depression and mortality in type 2 diabetes mellitus. *Diabetes Metab J*. 2017;41(4):263–264.
11. McIntyre E, Lauche R, Frawley J, et al. Physical activity and depression symptoms in women with chronic illness and the mediating role of health-related quality of life. *J Affect Disord*. 2019;252:294–299.
12. Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care*. 2008;31(12):2383–2390.
13. Eaton WW, Armenian H, Gallo J, et al. Depression and risk for onset of type II diabetes. a prospective population-based study. *Diabetes Care*. 1996;19(10):1097–1102.
14. Nouwen A, Winkley K, Twisk J, et al; European Depression in Diabetes (EDID) Research Consortium. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia*. 2010;53(12):2480–2486.
15. Cuijpers P, Vogelzangs N, Twisk J, et al. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry*. 2014;171(4):453–462.
16. Khan A, Fahl Mar K, Gokul S, et al. Mortality during US FDA clinical trials in patients with diabetes, hypertension, depression and schizophrenia. *World J Biol Psychiatry*. 2020;21(1):64–71.
17. Gonzalez JS, Safren SA, Cagliero E, et al. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. *Diabetes Care*. 2007;30(9):2222–2227.
18. Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. *Gen Hosp Psychiatry*. 2013;35(3):217–225.
19. Crosby A, Gfroerer J, Han B, Ortega L, Parks SE. Suicidal thoughts and behaviors among adults aged ≥18 Years–United States, 2008-2009. CDC website. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss6013a1.htm?=nocontent. 2011.
20. Ribeiro JD, Huang X, Fox KR, et al. Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies. *Br J Psychiatry*. 2018;212(5):279–286.
21. Goodwin RD, Marusic A, Hoven CW. Suicide attempts in the United States: the role of physical illness. *Soc Sci Med*. 2003;56(8):1783–1788.
22. Oquendo MA, Lizardi D, Greenwald S, et al. Rates of lifetime suicide attempt and rates of lifetime major depression in different ethnic groups in the United States. *Acta Psychiatr Scand*. 2004;110(6):446–451.
23. Myers AK, Grannemann BD, Lingvay I, et al. Brief report: depression and history of suicide attempts in adults with new-onset Type 2 Diabetes. *Psychoneuroendocrinology*. 2013;38(11):2810–2814.
24. Webb RT, Kontopantelis E, Doran T, et al. Suicide risk in primary care patients with major physical diseases: a case-control study. *Arch Gen Psychiatry*. 2012;69(3):256–264.
25. Druss B, Pincus H. Suicidal ideation and suicide attempts in general medical illnesses. *Arch Intern Med*. 2000;160(10):1522–1526.
26. Pompili M, Lester D, Innamorati M, et al. Quality of life and suicide risk in patients with diabetes mellitus. *Psychosomatics*. 2009;50(1):16–23.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613–619.
28. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130–1139.
29. Austin PC. The performance of different propensity-score methods for estimating relative risks. *J Clin Epidemiol*. 2008;61(6):537–545.
30. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika*. 1993;80(3):557–572.
31. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer; 2000.
32. Wyatt LC, Ung T, Park R, et al. Risk Factors of Suicide and Depression among Asian American, Native Hawaiian, and Pacific Islander Youth: A Systematic Literature Review. *J Health Care Poor Underserved*. 2015;26(suppl):191–237.
33. Nock MK, Hwang I, Sampson NA, et al. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15(8):868–876.
34. Lin EH, Heckbert SR, Rutter CM, et al. Depression and increased mortality in diabetes: unexpected causes of death. *Ann Fam Med*. 2009;7(5):414–421.
35. van Dooren FE, Nefs G, Schram MT, et al. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2013;8(3):e57058.
36. Richardson LK, Egede LE, Mueller M. Effect of race/ethnicity and persistent recognition of depression on mortality in elderly men with type 2 diabetes and depression. *Diabetes Care*. 2008;31(5):880–881.
37. Novak M, Mucsi I, Rhee CM, et al. Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression. *Diabetes Care*. 2016;39(11):1940–1947.
38. Naicker K, Johnson JA, Skogen JC, et al. Type 2 Diabetes and Comorbid Symptoms of Depression and Anxiety: Longitudinal Associations With Mortality Risk. *Diabetes Care*. 2017;40(3):352–358.
39. Pan A, Lucas M, Sun Q, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. *Arch Intern Med*. 2010;170(21):1884–1891.
40. Bruce DG, Davis WA, Starkstein SE, et al. A prospective study of depression and mortality in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia*. 2005;48(12):2532–2539.
41. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care*. 2005;28(11):2668–2672.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Mortality and Suicide Related to Major Depressive Disorder Before and After Type 2 Diabetes Mellitus

Author(s): Chun-Jen Huang, MD, MPH, PhD; Yu-Ting Huang, MS; Pai-Cheng Lin, MD, MS; Hui-Min Hsieh, PhD; and Yi-Hsin Yang, PhD

DOI Number: https://doi.org/10.4088/JCP.20m13692

List of Supplementary Material for the article

1. Table 1 Chronic Comorbidities and ICD-9-CM code defined in this study
2. Table 2 Demographic status, comorbidity and outcome compared in matched I cohort
3. Table 3 Demographic status, comorbidity and outcome compared in matched II cohort

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1 Chronic Comorbidities and ICD-9-CM code defined in this study

Chronic complications in this study	ICD-9-CM codes
● Neurological disease	
Myasthetic syndromes in disease classified elsewhere (amyotrophy)	358.1
Others specified idiopathic peripheral neuropathy	
Mononeuritis of upper and lower limbs	356.8
Arthropathy associated w/neurological disorders (Charcot's	354,355
arthropathy)	713.5
Peripheral autonomic neuropathy	
Polyneuropathy in diabetes	337.1
Neuralgia, neuritis, and radiculitis, unspecified	357.2
Diabetes with neurological complications	729.2
Occlusion of cerebral arteries	250.6
Hemorrhagic stroke	434
Late effects of cerebrovascular disease	430-432
Occlusion of stenosis of pre-cerebral arteries	438
Other and ill-defined cerebrovascular disease	433
Acute, but ill-defined, cerebrovascular disease	437
Transient ischemic attack	436
● Peripheral vascular disease	435
Atherosclerosis	
Embolism and thrombosis, structure of artery	440
Other peripheral vascular disease	444,447.1
Other disorders of circulatory system	443
Phlebitis and thrombophlebitis, portal vein thrombosis, and	459
thrombolism and venous thrombolism	451,452
Other venous embolism and thrombolism	
Varicose veins of lower extremities	453
Gangrene and amputations	454
Chronic ulcer of skin	785.4,885-887,895-897
● Cardiovascular disease	707
Aortic and other aneurysms	
Hypotension	441,442
Angina	458
Conduction disorders and cardiac dysrhythmias	413
Atherosclerotic cardiovascular disease	426-427
	429.2
Chronic complications	ICD-9-CM codes

Cardiomegaly	429.3
Cardiomyopathy	425
Other acute and subacute forms of ischemic heart disease	411
Heart failure	
Diabetes w/peripheral circulatory disorders	428
Myocardial degeneration	250.7
Myocardial infarction	429.1
Other chronic ischemic heart disease	410,412
Hypertension	414
● Renal complications	401-405
Infections of kidney	
Other disorders of bladder	590
Cystitis	596
Renal sclerosis, unspecified	595
Glomerulonephritis, nephritic syndrome, nephritis, nephropathy	587
Proteinuria	580-583
Renal failure and its sequelae	
Other disorders of kidney and ureter	791.0
Urinary tract infection	584,586,588
Diabetes and renal complications	593
Chronic renal failure (end-stage renal disease)	599.0
● Endocrine/metabolic complications	250.4
Dwarfism-obesity syndrome	585
Glycogenosis and galactosemia	
Disorders of iron metabolism	259.4
Hypercholesterolemia	271.0,271.1
Hyperchylomicronemia	275.0
Hyperkalemia	272.0
Hypertriglyceridemia	272.3
Macroglobulinemia	276.7
Lancereaux's disease	272.1
Lipidoses	273.3
Other specified endocrine disorders	261
	272.7
	259.8

Chronic complications	ICD-9-CM codes
Other and unspecified hyperlipidemia	272.4
Mixed hyperlipidemia	272.2

Renal glycosuria	271.4
● Ophthalmic complications	
Other retinal disorders	362
Vascular disorders of the iris and ciliary body	364.0,364.4
Disorders of the optic nerve and visual pathways	377
Diabetes with ophthalmic complications	250.5
Cataract	366
Glaucoma	365
Visual disturbance, low vision, blindness	368-369
● Other complications	
Bacteremia, bacterial infection, Coxsackie virus	079.2,790.7
Candidiasis of skin and nails	112.3
Chronic osteomyelitis of the foot	730.17
Other and unspecified noninfectious gastroenteritis and colitis	558.9
Impotence of organic origin	
Infective otitis externa	607.84
Degenerative skin disorders	380.1
Candidiasis of vulva and vagina	709.3
Cellulites	112.1
Diabetes with other specified manifestations	681,682
Diabetes with unspecified complication	250.8
Other bone involvement in disease classified elsewhere	250.9
	731.8

Supplementary Table 2. Demographic status, comorbidity and outcome compared in matched I cohort

			MDD before T2DM		T2DM without MDD		P-value
variable	class	total	N	%	N	%	
Total		13190	2638	20.0	10552	80.0	
Sex	Male	5165	1033	39.2	4132	39.2	1
	Female	8025	1605	60.8	6420	60.8	
Age		13190	57.17±14.00		57.17±13.71		1
Income	0	3210	620	23.5	2590	24.6	0.0003
	0-19200	2443	561	21.3	1882	17.8	
	>=19200	7537	1457	55.2	6080	57.6	
Region	0	264	45	1.7	219	2.1	0.0001
	Northern	5884	1174	44.5	4710	44.6	
	Central	2253	388	14.7	1865	17.7	
	Southern	4398	963	36.5	3435	32.5	
	Eastern	391	68	2.6	323	3.1	
Education level	primary school	6261	1219	46.2	5042	47.8	0.0408
	Secondary school	2332	514	19.5	1818	17.2	
	High school	2855	574	21.8	2281	21.6	
	University above	1742	331	12.5	1411	13.4	
Marital status	unmarried	1500	334	12.7	1166	11.0	0.0000
	married	9692	1843	69.9	7849	74.4	
	divorce/Spouse dies	1998	461	17.4	1537	14.6	
CCI score	mean±SD	13190	2.57±2.06		2.75±2.29		0.0002
CCI index	0	1720	369	14.0	1351	12.8	0.1132
	1	2555	529	20.1	2026	19.2	
	>=2	8915	1740	66.0	7175	68.0	
Comorbidities							

Neurological disease	6365	1259	47.7	5106	48.4	0.5400
Peripheral vascular disease	2203	452	17.1	1751	16.6	0.5059
Cardiovascular disease	9895	1953	74.0	7942	75.3	0.1911
Renal disease	7739	1518	57.5	6221	59.0	0.1877
Endocrine/metabolic disease	6091	1230	46.6	4861	46.1	0.6044
Ophthalmic disease	5253	1052	39.9	4201	39.8	0.9527
GAD	1825	401	15.2	1424	13.5	0.0232
Outcomes						
All-cause mortality	2540	525	19.9	2015	19.1	0.3461
Committed Suicide	41	23	0.9	18	0.2	<0.0001
Suicide attempt	17	13	0.5	4	0.0	<0.0001
Suicide behavior	58	36	1.4	22	0.2	<0.0001

T2DM: Type 2 diabetes mellitus, MDD: Major Depressive Disorder

CCI: Charlson Comorbidity Index, GAD: General anxiety disorder

Supplementary Table 3. Demographic status, comorbidity and outcome compared in matched II cohort

			MDD after T2DM		T2DM without MDD		P-value
variable	class	total	N	%	N	%	
Total		25570	5114	20.0	20456	80.0	
Sex	Male	9915	1983	38.8	7932	38.8	1
	Female	15655	3131	61.2	12524	61.2	.
Age		25570	58.07±12.5		58.07±12.6		1
Income	0	7240	1460	28.5	5780	28.3	0.0008
	0-19200	4752	1036	20.3	3716	18.2	.
	>=19200	13578	2618	51.2	10960	53.6	.
Region	0	552	95	1.9	457	2.2	0.0004
	Northern	11216	2165	42.3	9051	44.2	.
	Central	4520	869	17.0	3651	17.8	.
	Southern	8493	1802	35.2	6691	32.7	.
	Eastern	789	183	3.6	606	3.1	.
Education level	primary school	15396	3001	58.7	12395	60.6	0.0439
	Secondary school	3923	839	16.4	3084	15.1	.
	High school	4187	862	16.9	3325	16.3	.
	University above	2064	412	8.1	1652	8.1	.
Marital status	unmarried	1894	375	7.3	1519	7.4	0.0161
	married	19394	3814	74.6	15580	76.2	.
	divorce/Spouse dies	4282	925	18.1	3357	16.4	.
CCI score	mean±SD	25570	1.43±1.8		1.32±1.7		0.0001
CCI index	0	11180	2160	42.2	9020	44.1	0.0222
	1	5435	1084	21.2	4351	21.3	.
	>=2	8954	1870	36.6	7084	34.6	.

Comorbidities						
Neurological disease	6018	1276	25.0	4742	23.2	0.0077
Peripheral vascular disease	1711	397	7.8	1314	6.4	0.0006
Cardiovascular disease	12643	2600	50.8	10043	49.1	0.0254
Renal disease	7587	1592	31.1	5995	29.3	0.0107
Endocrine/metabolic disease	6163	1275	24.9	4888	23.9	0.1212
Ophthalmic disease	5719	1174	23.0	4545	22.2	0.2582
GAD	887	177	3.5	710	3.5	0.9773
Outcomes						
All-cause mortality	5694	1675	32.8	4019	19.6	<0.0001
Committed Suicide	81	63	1.2	18	0.1	<0.0001
Suicide behavior	94	75	1.5	19	0.1	<0.0001

T2DM: Type 2 diabetes mellitus, MDD: Major Depressive Disorder
CCI: Charlson Comorbidity Index, GAD: General anxiety disorder
*Since suicide attempt number is too small, so the analysis only conduct all-cause mortality ,Committed Suicide and Suicide behavior