

# Depression, Diabetes Mellitus and Mortality in Older Adults: A National Cohort Study in Taiwan

Vincent Chin-Hung Chen<sup>1,2</sup>, Tsu-Nai Wang<sup>3</sup>, Ming-Chia Hsieh<sup>4</sup>, Shih-Yong Chou<sup>1</sup>, Meng-Chih Lee<sup>5,6</sup>, Roger S McIntyre<sup>7</sup>, Mong-Liang Lu<sup>8</sup>, Yin-To Liao<sup>9,10</sup>, Chih-Jung Yeh<sup>11,12</sup>

<sup>1</sup>Department of Psychiatry, Chang Gung Medical Foundation, Chiayi Chang Gung Memorial Hospital, Chiayi, Taiwan; <sup>2</sup>School of Medicine, Chang Gung University, Taoyuan, Taiwan; <sup>3</sup>Department of Public Health, College of Health Science, Kaohsiung Medical University, Kaohsiung, Taiwan; <sup>4</sup>U Come Joint Clinic, Taichung, Taiwan; <sup>5</sup>Department of Family Medicine, Taichung Hospital, Taichung, Taiwan; <sup>6</sup>College of Management, Chaoyang University of Technology, Taichung, Taiwan; <sup>7</sup>University of Toronto, Toronto, ON, Canada; <sup>8</sup>Department of Psychiatry, Wan-Fang Hospital and School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; <sup>9</sup>Department of Psychiatry, Chung Shan Medical University Hospital, Taichung, Taiwan; <sup>10</sup>Department of Psychiatry, School of Medicine, Chung Shan Medical University, Taichung, Taiwan; <sup>11</sup>Institute of Population Health Sciences, National Health Research Institutes, Taipei, Taiwan; <sup>12</sup>School of Public Health, Chung Shan Medical University, Taichung, Taiwan

Correspondence: Yin-To Liao, Email [je2tezy@yahoo.com.tw](mailto:je2tezy@yahoo.com.tw); Chih-Jung Yeh, School of Public Health, Chung Shan Medical University, No. 110, Section I, Jianguo N. Road, Taichung, 402, Taiwan, Tel +886-4-24730022x12183, Fax +886-4-23248179, Email [alexeyeh@csmu.edu.tw](mailto:alexeyeh@csmu.edu.tw)

**Purpose:** Diabetes mellitus (DM) increases the risk of cardiovascular and all-cause mortality. The coexistence of depression and DM is associated with an increased risk of DM complications and functional morbidity. The independent effect of depression on mortality in patients with DM is unclear, and relevant Asian studies have provided inconsistent results. Accordingly, this study assessed the independent and additive effects of DM and depression on mortality in a nationally representative cohort of older adults in Taiwan over a 10-year observation period.

**Patients and Methods:** A total of 5041 participants aged 50 years or older were observed between 1996 and 2007. We defined depression as a score of  $\geq 8$  on the 10-item Center for Epidemiologic Studies Depression (CES-D 10) scale. Additionally, we defined participants as having type 2 DM if they had received a diagnosis of type 2 DM from a health-care provider. Cox proportional hazard models were applied to analyze predictors of mortality in depression and DM comorbidity groups.

**Results:** During the 10-year follow-up period, 1637 deaths were documented. After adjustment for potential confounders, the hazard ratios for mortality in participants with both depression and DM, DM only, and depression only were 2.47 (95% confidence interval [CI]: 2.02–3.03), 1.95 (95% CI: 1.63–2.32), and 1.23 (95% CI: 1.09–1.39), respectively.

**Conclusion:** The co-occurrence of depression with DM in Asian adults increased overall mortality rates. Our results indicate that the increased mortality hazard in individuals with DM and depression was independent of sex.

**Keywords:** diabetes mellitus, depression, mortality, cohort

## Introduction

Cross-sectional and longitudinal epidemiological studies have consistently reported a relatively high prevalence of depression in patients with diabetes. Depressive disorder affects approximately 20% to 25% of patients with diabetes mellitus (DM), and this rate is nearly twice that observed in individuals without DM.<sup>1</sup> Depression was also reported to be associated with poor adherence to self-care regimens in patients with DM, including adherence to glucose monitoring, diet, exercise regimens, and medication prescriptions.<sup>2</sup> Moreover, depression coexisting with DM is positively associated with psychosocial and workplace impairment.<sup>3</sup> Depression is strongly associated with the presence of Framingham risk factors (ie, smoking, obesity, and sedentary lifestyle) for cardiovascular disease in patients with DM.<sup>4</sup> Neurobiologically, depression affects multiple effector systems implicated in the DM disease process. Depression is also associated with the dysregulation of the hypothalamic–pituitary–adrenal axis (HPA)<sup>5</sup> and sympathetic nervous system<sup>6,7</sup> and with an increase in inflammatory markers,<sup>8,9</sup> which may adversely affect the course of DM. Such neurobiological changes in depression have also been observed in DM.

Both depression and DM are associated with an increased risk of all-cause mortality.<sup>10,11</sup> A study of older adults in Taiwan revealed that depressive symptoms constituted an independent risk for all-cause mortality in men (hazard ratio [HR], 1.27; 95% CI, 1.03–1.56).<sup>12</sup> Comorbid depression is associated with relatively high mortality rates among patients with diabetes.<sup>13–15</sup> However, existing studies on this topic are limited by their small sample sizes, short-term follow-up periods, and inclusion of only patients with diabetes (with no comparison group of individuals without diabetes).<sup>16</sup> Furthermore, few studies have compared mortality rates between adults with mood disorders without DM, adults with DM and no concurrent mood disorders, and adults with both depression and DM.<sup>13</sup>

Few studies have provided evidence of relatively high mortality in patients with both depression and DM in non-Western Countries.<sup>14</sup> A study conducted in Hong Kong identified no increased risk of mortality in patients with concurrent depression and DM when compared with those without concurrent depression and DM.<sup>17</sup> The comparable mortality rates between patients with diabetes with and without concurrent depression in the aforementioned study are inconsistent with the findings of studies conducted in Western countries. Therefore, evaluating the influence of depression in patients with DM in a separate Asian population is appealing. Accordingly, we conducted this study to determine whether the coexistence of depression and DM would result in an increased risk of mortality when compared with the existence of either DM or depression alone. We used an extensive nationally representative database in Taiwan to conduct the analysis.

## Materials and Methods

### Study Population and Data Collection

The Survey of Health and Living Status of the Elderly in Taiwan (SHLSET) is a population-based longitudinal follow-up study conducted by the Bureau of Health Promotion, Department of Health in Taiwan. The SHLSET started in 1989 and had subsequent follow-up waves in 1993, 1996, 1999, 2003, and 2006.<sup>18</sup> Its broad objective was to provide data regarding demographics, physical condition, socioeconomic status, health behaviors, and lifestyle in older adults. Sample selection was conducted using a randomized, stratified sampling scheme in individuals aged  $\geq 60$  years. The sample size of the SHLSET cohort in 1989 was 4049 participants aged between 60 and 96 years. Data were collected through face-to-face interviews, and the survey response rate was 91.8%. In 1996, the original sample decreased to 2669 (owing to 1047 deaths and 333 participants lost to follow-up). Hence, the same sampling method was used to recruit 2462 respondents aged  $\geq 50$  years, who constituted a new sample panel. Thus, the cohort was extended to include adults aged  $\geq 50$  years. The 10-item Center for Epidemiologic Studies Depression (CES-D) scale had been used in the SHLSET since 1996 for data collection. Data on depressive symptoms were collected in the follow-up waves in 1996, 1999, 2003, and 2006. In Taiwan, DM is diagnosed in accordance with the guidelines stipulated by the American Diabetes Association. The diagnosis was made by a board-certified physician and reviewed by the National Health Insurance Bureau's panel of related medical experts. Participants provided self-reports of physician diagnoses of DM and depression. To estimate mortality rates, we selected the original and newly added samples in the 1996 wave of the SHLSET as the baseline sample and followed the corresponding participants until the end of 2007. Specifically, 5041 participants were followed from 1996 until the end of 2007. Among the participants, 427 were removed from the multiple proportional hazard regression model because of missing data in the following categories: demographics, healthy lifestyle, six major diseases (hypertension, heart disease, stroke, DM, lung disease, and cancer), depressive symptom score, self-rated health status, and disability in activities of daily living (ADL).

The participants' demographic characteristics, including age, sex, education level, and marital status, were included in the survey. Marital status was categorized as married (currently living with a spouse) or single (not living with a spouse). Education level was categorized into four groups: illiterate, elementary school, high school, and college/graduate school. We examined three health-related behaviors. Cigarette smoking behavior was categorized as current smokers and never/former smokers. Participants who drank alcohol at any frequency were defined as current drinkers. Exercise frequency was divided into regular exercise ( $\geq 3$  times a week) and irregular exercise ( $< 3$  times a week).

Depressive symptoms were measured using the short-form 10-item CES-D scale. A CES-D score of  $\geq 8$  was considered to indicate depression.<sup>19</sup> The co-occurrence of DM, hypertension, coronary heart disease, stroke, cancer,

and lung disease was identified using medical claims data that were based on physician-established diagnoses. Self-rated health was categorized into the following categories according to the participants' self-perceived state of health at the time of the survey: good (excellent, good, or fair) and poor (poor or very poor). Disability in ADL was defined as the presence of a disability affecting any of the following areas: eating, dressing, transferring, bathing, walking indoors, or using the toilet. The national identification number of each of the recruited participants during the study period was imported into the National Death Registration System to detect mortality. To investigate the association between comorbidities and mortality, we divided the participants into four groups: group 1, comprising participants without depression or DM; group 2, comprising participants with depression but not DM (ie, depression alone); group 3, comprising participants with DM but not depression (ie, DM alone); and group 4, comprising participants with depression and DM (depression and DM).

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital. Written informed consent was obtained from all participants. The study protocol was in accordance with the Declaration of Helsinki.

## Statistical Analysis

We used Student's *t*-test or chi-square statistics to compare the baseline characteristics between the groups. Cox proportional hazards models were applied to analyze the predictors of mortality in the groups. Multivariate analyses were conducted using four models that were adjusted for potential confounders: demographics, healthy behaviors, disease morbidity, self-rated health, and disability in ADL. Moreover, multiple Cox regression analyses were conducted using four model settings: model A was adjusted for demographic variables (age, sex, educational level, and marital status); model B included the same variables as those in model A, in addition to including variables related to healthy behaviors (cigarette smoking, alcohol drinking, and regular exercise); model C included the same variables as those in model B, in addition to including variables related to health status (number of diseases and self-rated health); and model D included the same variables as those in model C, in addition to including variables related to disability in ADL. We assessed the goodness of fit for the models by using the Akaike information criterion (AIC). The AIC can be used to correct the deviations for a certain number of parameters by penalizing models with many extra parameters, and it can be derived as follows:

$AIC = D + 2p$  where  $p$  represents the number of parameters and  $D$  represents the deviance. A lower AIC value indicates a better model fit.

All statistical analyses were conducted using SAS (version 9.2; SAS Institute, Cary, N.C.). Statistical significance was set at a two-tailed  $p$  value of  $<0.05$ .

## Results

During the 10-year follow-up period, 1637 deaths were documented among 4614 participants (29.2%). The characteristics of the participants in the four groups are presented in Table 1. Of the four groups, group 4 had the highest mortality rate. The four groups differed significantly in terms of age, years of follow-up, number of diseases, pain, age distribution, sex, education level, marital status, cigarette smoking, alcohol drinking, regular exercise, six major diseases, cognition, disability, and self-rated health (Table 1).

Figure 1 presents the survival curves for the four groups. Groups 1 and 4 had the highest and lowest survival probabilities, respectively. Group 3 had a higher survival probability than did group 2 in the first 6–7 years of follow-up, but this was switched in the subsequent years. The 5-year survival probabilities observed for groups 1, 2, 3, and 4 were 90%, 80%, 84%, and 60%, respectively.

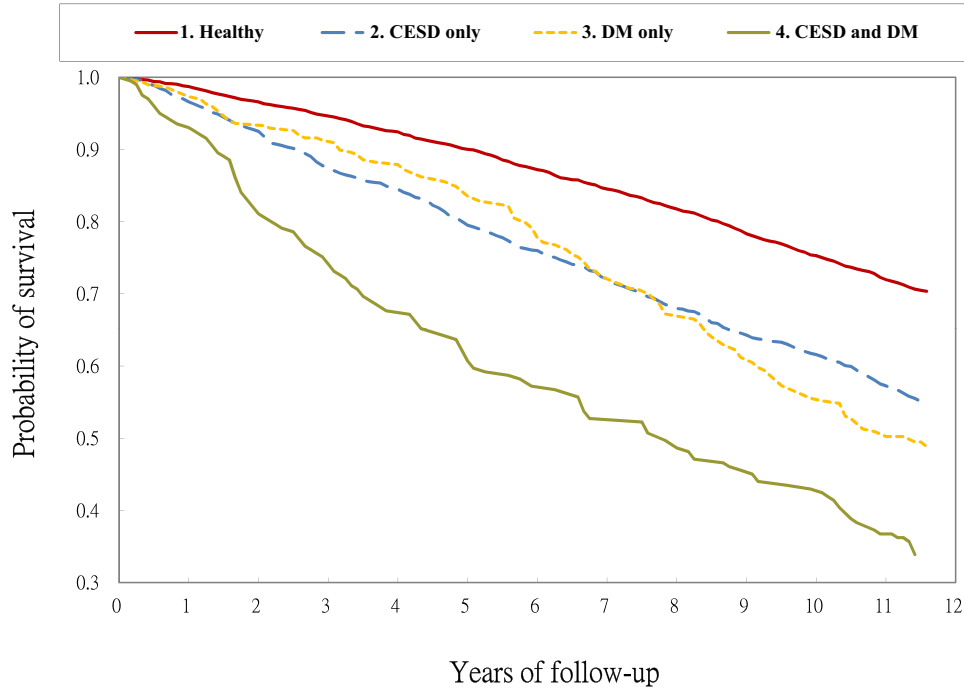
We conducted a univariate analysis to adjust for confounding variables. Table 2 presents the predictors of mortality in the four groups, as determined using multiple Cox regression; moreover, AIC values were derived for model comparison. In model A, mortality was significantly higher in group 4 than in the other groups ( $HR = 3.35$ ). Compared with group 1, groups 2 and 3 had significantly higher mortality ( $HRs\ 1.51 =$  and  $2.02$ , respectively) after adjustment for confounding demographic variables. We observed similar results for model B and C, with further adjustment for healthy behavior variables, cigarette smoking and alcohol drinking, health status variables, number of diseases, and self-rated health.

**Table I** Subjects' Characteristics Among Depression and Diabetes Mellitus Groups in Year 1996

	Total (N=4614)		No Depression, No DM (N=2944)		No DM, With Depression (N=1174)		No Depression, With DM (N=298)		Depression and DM (N=198)		P value
	Mean/n	SD/(%)	Mean/n	SD/(%)	Mean/n	SD/(%)	Mean/n	SD/(%)	Mean/n	SD/(%)	
No. of death; Mortality	1637	29.2%	845	28.7%	516	44.0%	148	49.7%	128	64.7%	<0.0001
Age (in years)	65.7	9.1	64.7	9.1	68.0	9.3	66.0	8.2	67.5	7.5	<0.0001
Years of Follow-Up	9.4	3.3	9.8	3.0	8.7	3.7	8.8	3.4	7.1	4.2	<0.0001
Numbers of diseases	0.54	0.78	0.43	0.68	0.71	0.88	0.68	0.78	1.09	1.06	<0.0001
Pains	1.53	0.79	1.34	0.61	1.92	0.92	1.44	0.71	2.28	1.10	<0.0001
Age 50–59	1387	30.1%	1005	34.1%	260	22.2%	82	27.5%	40	20.2%	<0.0001
Age 60–64	617	13.4%	407	13.8%	141	12.0%	43	14.4%	26	13.1%	
Age 65–69	905	19.6%	582	19.8%	215	18.3%	68	22.8%	40	20.2%	
Age 70–74	913	19.8%	520	17.7%	271	23.1%	60	20.1%	62	31.3%	
Age 75+	792	17.2%	430	14.6%	287	24.5%	45	15.1%	30	15.2%	
Female	2133	46.2%	1210	41.1%	656	55.9%	148	49.7%	119	60.1%	<0.0001
Male	2481	53.8%	1734	58.9%	518	44.1%	150	50.3%	79	39.9%	
Educational level											<0.0001
Illiterate	1456	31.5%	746	25.3%	533	45.4%	84	28.2%	93	47.0%	
Elementary	2124	46.0%	1426	48.4%	481	41.0%	135	45.3%	82	41.4%	
High School	773	16.8%	570	19.4%	122	10.4%	64	21.5%	17	8.6%	
Above college	261	5.7%	202	6.9%	38	3.2%	15	5.0%	6	3.0%	
Marital status											
Without spouse	1295	28.1%	685	23.3%	464	39.5%	81	27.2%	65	32.8%	<0.0001
With spouse	3319	71.9%	2259	76.7%	710	60.5%	217	72.8%	133	67.2%	
Cigarette smoking											
No	3356	72.7%	2076	70.5%	893	76.1%	230	77.2%	157	79.3%	<0.0001
Yes	1258	27.3%	868	29.5%	281	23.9%	68	22.8%	41	20.7%	
Alcohol drinking											
No	3620	78.5%	2213	75.2%	988	74.2%	242	81.2%	177	89.4%	<0.0001
Yes	994	21.5%	731	24.8%	186	15.8%	56	18.8%	21	10.6%	
Regular exercising											
No	2442	52.9%	1417	48.1%	771	65.7%	138	46.3%	116	58.9%	<0.0001
Yes	2170	47.1%	1527	51.9%	402	34.3%	160	53.7%	81	41.1%	
Hypertension											
No	3422	74.2%	2304	78.3%	833	70.9%	179	60.1%	106	53.5%	<0.0001
Yes	1192	25.8%	640	21.7%	341	29.1%	119	39.9%	92	46.5%	
Coronary Heart Disease											
No	3944	85.5%	2627	89.2%	938	79.9%	243	81.5%	136	68.7%	<0.0001
Yes	670	14.5%	317	10.8%	236	20.1%	55	18.5%	62	31.3%	

Stroke											
No	4462	96.7%	2883	97.9%	1112	94.7%	288	96.6%	179	90.4%	<0.0001
Yes	152	3.3%	61	2.1%	62	5.3%	10	3.4%	19	9.6%	
Kidney Disease											
No	4302	93.4%	2828	96.3%	1054	89.8%	271	91.2%	149	75.6%	<0.0001
Yes	302	6.6%	108	3.7%	120	10.2%	26	8.8%	48	24.3%	
Cancer											
No	4557	98.8%	2918	99.1%	1156	98.5%	295	99.0%	188	94.9%	<0.0001
Yes	57	12%	26	0.9%	18	1.5%	3	1.0%	10	5.1%	
Lung Disease											
No	4181	90.6%	2730	92.7%	1003	85.4%	283	95.0%	165	83.3%	<0.0001
Yes	433	9.4%	214	7.3%	171	14.6%	15	5.0%	33	16.7%	
Pain											
No	1848	89.9%	2817	95.7%	916	78.1%	279	93.9%	136	68.7%	<0.0001
Yes	464	10.1%	127	4.3%	257	21.9%	18	6.1%	62	31.3%	
Cognitive function											
Fair	1817	78.4%	1117	83.4%	493	69.5%	128	85.3%	79	66.9%	<0.0001
Poor	500	21.6%	223	16.6%	216	30.5%	22	14.7%	39	33.1%	
IADL disability											
No	3174	69.0%	2365	80.6%	547	46.7%	199	66.8%	63	31.8%	<0.0001
Yes	1428	31.0%	570	19.4%	624	53.3%	99	33.2%	135	68.2%	
ADL disability											
No	4420	95.8%	2914	99.0%	1050	89.4%	292	98.0%	164	82.8%	<0.0001
Yes	194	4.2%	30	1.0%	124	10.6%	6	2.0%	34	17.2%	
Self-rated health											
Poor	1349	29.2%	486	16.5%	616	52.5%	105	35.2%	142	71.7%	<0.0001
Good	3265	70.8%	2458	83.5%	558	47.5%	193	64.3%	56	28.3%	

**Abbreviations:** DM, diabetes mellitus; IADL, Instrumental activities of daily living; ADL, activities of daily living.



**Figure 1** Survival curve among depression and DM comorbidity groups.

Model D had the lowest AIC (25484.8) among all four models, indicating that it was the most accurate. For model D, after adjustment for all confounders, the HRs derived for the groups 4, 3, and 2 were 2.47 (95% confidence interval [CI]: 2.02–3.03), 1.95 (95% CI: 1.63–2.32), and 1.23 (95% CI: 1.09–1.39), respectively (Table 2).

**Table 2** Predictors of Mortality Among Depression and Diabetes Mellitus Comorbidity Groups Using Multiple Cox Regression

	Model A			Model B			Model C			Model D		
	HR	95% C.I.		HR	95% C.I.		HR	95% C.I.		HR	95% C.I.	
Depression alone vs Normal	1.51	1.35	1.69	1.48	1.32	1.66	1.29	1.14	1.45	1.23	1.09	1.39
DM alone vs Normal	2.02	1.69	2.40	2.05	1.72	2.45	1.94	1.62	2.31	1.95	1.63	2.32
Depression + DM vs Normal	3.35	2.78	4.05	3.31	2.74	3.99	2.62	2.15	3.20	2.47	2.02	3.03
Age 60–64 vs Age 50–59	1.64	1.31	2.06	1.61	1.29	2.02	1.58	1.26	1.98	1.57	1.25	1.97
Age 65–69 vs Age 50–59	2.62	2.18	3.16	2.56	2.13	3.08	2.49	2.07	3.00	2.46	2.04	2.96
Age 70–74 vs Age 50–59	4.11	3.45	4.90	3.94	3.30	4.70	3.70	3.09	4.42	3.64	3.04	4.36
Age 75+ vs Age 50–59	8.62	7.26	10.23	8.06	6.75	9.63	7.82	6.54	9.35	7.60	6.36	9.09
Male vs Female	1.91	1.71	2.14	1.87	1.64	2.13	1.88	1.65	2.14	1.88	1.65	2.14
Elementary school vs Illiterate	0.88	0.78	0.99	0.89	0.79	1.00	0.89	0.79	1.00	0.90	0.80	1.02
Junior or senior school vs Illiterate	0.65	0.55	0.77	0.70	0.59	0.83	0.71	0.60	0.84	0.71	0.60	0.85
Above college vs Illiterate	0.56	0.43	0.72	0.62	0.48	0.80	0.64	0.49	0.82	0.65	0.50	0.84
With vs Without spouse				0.82	0.73	0.91	0.82	0.73	0.91	0.81	0.73	0.91
Cigarette smoking (Yes vs No)				1.30	1.15	1.47	1.33	1.18	1.50	1.33	1.18	1.50
Alcohol drinking (Yes vs No)				0.79	0.69	0.91	0.83	0.73	0.95	0.84	0.74	0.96
No. of disease							1.12	1.06	1.19	1.09	1.03	1.16
Self-rated health (Good vs Poor)							0.74	0.66	0.82	0.78	0.69	0.87
ADL disability (Yes vs No)										2.21	1.85	2.64
Model Fitting Statistics (AIC)	N=4614 AIC=25632.7			N=4614 AIC=25598.0			N=4614 AIC=25547.6			N=1614 AIC=25484.8		

**Abbreviations:** DM, diabetes mellitus; ADL, activities of daily living.



In model D, other significant mortality risk factors were older age, the male sex, living without a spouse, cigarette smoking, and having a relatively high number of diseases, poor self-rated health, disability in ADL, a lower education level, and no alcohol intake. We also performed a stratification analysis to investigate the effects of depression and DM comorbidity on mortality risks in the context of other major diseases ([Supplementary Table 1](#)).

## Discussion

Our epidemiological study is the first to investigate whether coexistence of depression and DM would result in an increased risk of mortality when compared with the existence of either DM or depression alone in older Asian patients. The main findings of our study are that the HR for mortality in patients with depression alone, DM alone, and both depression and DM were 1.23 (95% CI: 1.09–1.39), 1.95 (1.63–2.32), and 2.47 (2.02–3.03), respectively. DM alone and depression alone were risk factors for mortality; however, having both depression and DM led to a much higher mortality risk. The effects on mortality from depression alone, DM alone, and both depression and DM were independent of sex.

Our results are consistent with those reported by Egede,<sup>20</sup> who reported depression coexisting with DM to be associated with an increased risk of mortality among 10,025 participants in the population-based National Health and Nutrition Examination Survey conducted in the United States over an 8-year observation period. In the aforementioned study, the HRs for mortality in patients with depression alone, DM alone, and both depression and DM were 1.20 (95% CI: 1.03–1.40), 1.88 (1.55–2.27), and 2.50 (2.04–3.08), respectively, compared with that in patients without depression or DM. These findings are consistent with our findings. A previous study that used SHLSET data also revealed that depressive symptoms and DM increased mortality risk in older adults.<sup>12</sup> The mentioned study indicated that depressive symptoms increased mortality risk in men, not in women; however, the study did not investigate the effects of the interaction between DM and depression on mortality. Another study<sup>16</sup> investigated the individual and combined effects of depression and DM on all-cause mortality in 78,282 women who were registered nurses and aged 54–79 years during 2000–2006. The relative risks for all-cause mortality in women with depression alone, DM alone, and both DM and depression were 1.44 (95% CI: 1.34–1.54), 1.35 (95% CI: 1.21–1.51), and 2.07 (95% CI: 1.79–2.40), respectively, when compared with that in individuals without DM or depression. Moreover, the additional mortality hazard was confined only to female participants. In the present study, we investigated the additional mortality hazard in both sexes and observed an increased mortality hazard from depression, regardless of sex.

In our study, the HR for mortality in participants with DM increased by approximately twofold. The finding is consistent with those of previous studies that have reported a 1.5- to 2-fold increase in the risk of mortality.<sup>21–23</sup> However, our findings are not consistent with those of another study that reported 35% increase in the risk of mortality.<sup>16</sup> The discrepancy may partly be due to the differences in participant characteristics (age and sex), follow-up duration, and treatment. We also found that depression increased mortality risk by 23%. Pan et al revealed that depression caused a 40% increase in mortality risk in women with DM.<sup>16</sup> Two recent review studies have demonstrated that depression is linked to higher mortality rates among patients with DM (pooled HRs: 1.50, 95% CI: 1.35–1.66).<sup>13,15</sup> However, a study in Asia conducted by Lee et al indicated that veterans with depression and DM had lower 5-year age-adjusted mortality rates (OR: 6.50, 95% CI: 5.12–7.88) than did those with DM only (OR: 7.07, 95% CI: 6.75–7.39) when compared with the control group.<sup>24</sup> Another study conducted in Hong Kong reported that depression did not increase the risk of mortality in individuals with DM (HR: 0.96, 95% CI: 0.55–1.66).<sup>17</sup> These findings raise the question of whether the findings of additional risk from depression among Western patients with DM are applicable to Asian populations. Our results indicate that depression could increase mortality in patients with DM because the risk of mortality among patients with both depression and DM was higher than that among patients with DM alone. This finding is close to the additive risk of depression and DM. The difference between the findings of our study and those of the study by Lee et al. may be due to the longer follow-up duration in our study (11 years) when compared with that in the study by Lee et al (5 years), or it may be due to differences between the populations studied (older general population vs veterans).

Mechanisms that may mediate the observed increased mortality among patients with both DM and depression are unclear. A convergence of sociodemographic correlates, behavioral correlates, and other traditional risk factors has been found to affect both DM and mood disorders, eg, poor diet quality, sedentary lifestyle, inadequate exercise, and obesity.<sup>16</sup> Furthermore, DM and depression have a bidirectional relationship,<sup>25</sup> with both conditions sharing a common

pathogenetic nexus and many social and behavioral determinants.<sup>26</sup> For example, depression may result in discordance with diabetic treatment recommendations and a higher likelihood of unhealthy diet and suboptimal self-glucose monitoring. Poor self-care and blood sugar monitoring worsens blood sugar control and results in more long-term complications.<sup>27</sup> The disease burden of DM and its complications can negatively affect quality of life in patients and can increase disability, which may precipitate depression.<sup>3</sup> Furthermore, we can infer that DM-related cognitive difficulties, a deficit also noted in depression, may increase the risk of functional impairment and unhealthy behaviors.<sup>28</sup> Cerebrovascular events and other vascular changes in the brain related to DM may be correlated with depressive symptoms; this is because depression could trigger episodes of transient ischemia, decrease the cardiac fibrillation threshold, and promote platelet clumping and subsequent thrombosis.<sup>16,27</sup> A study reported that the combination of depression and DM may increase the risk of adverse cardiovascular mortality.<sup>29</sup>

This cohort study used a representative cross-national sample of older adults in Taiwan to compare mortality in patients with comorbid depression and DM with that in patients without depression or DM to clarify the combined effect of both disorders. The principal outcome (mortality) was obtained from the National Death Registration System Database, eliminating potential errors. In addition, research assistants collected the data using face-to-face interviews, rather than telephone interviews or mailed questionnaires, to ensure a higher response rate and accuracy level. We also controlled for several potential confounders, including smoking, alcohol, and other physical conditions.

## Limitations

Depression was assessed through a self-report survey rather than through a validated semistructured interview. However, research has indicated that self-reported depressive symptoms, corresponding to depressive episodes, are associated with mortality in individuals with DM.<sup>14</sup> We did not identify a relationship between markers of diabetic severity and overall mortality. In addition, we could not determine whether antidepressants moderated the mortality risk in this cohort. The sample encompassed people aged  $\geq 50$  years; therefore, our findings cannot be easily applied to other age populations.

## Conclusion

This study indicated that both depression and DM can increase mortality in older adults, and the combination of both disorders had an additional adverse effect on mortality in older adults. Because both are common, any individual with depression should be tested for DM (and vice versa). Whether treating both disorders simultaneously could lower mortality requires further investigation. In addition, additional longitudinal studies are necessary to investigate the mechanisms underlying the increased mortality rate caused by the combined effects of depression and DM.

## Abbreviations

DM, diabetes mellitus; CES-D 10, Center for Epidemiologic Studies Depression Scale; HPA, hypothalamic–pituitary–adrenal axis; SHLSET, Survey of Health and Living Status of the Elderly in Taiwan; ADA, American Diabetes Association; ADL, activities of daily living; AIC, Akaike Information Criterion.

## Data Sharing Statement

Due to legal restrictions, no dataset analyzed during this study was publicly available from the Bureau of Health Promotion, Department of Health in Taiwan. However, datasets are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital. Written informed consent was obtained from all participants.



## Acknowledgments

This study used data from the SHLSET database provided and managed by the Bureau of Health Promotion, Department of Health in Taiwan. The interpretations and conclusions presented herein do not represent those of the Bureau of Health Promotion, Department of Health.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This study was supported by grants (number CSH-2015-A-003) from Chung Shan Medical University Hospital, Taichung, Taiwan. The funding source had no role in the design, methods, subject recruitment, data collections, analysis, or preparation of the paper.

## Disclosure

Dr Roger S McIntyre reports grants from CIHR/GACD/National Natural Science Foundation of China (NSFC); personal fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie, and Atai Life Sciences; he is the CEO for Braxia Scientific Corp., outside the submitted work. The other authors report no conflicts of interest in this work.

## References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24(6):1069–1078. doi:10.2337/diacare.24.6.1069
2. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. *Diabetes Care*. 2004;27(9):2154–2160. doi:10.2337/diacare.27.9.2154
3. Lee Y, Smofsky A, Nykolation P, et al. Cognitive impairment mediates workplace impairment in persons with type 2 diabetes mellitus: results from the motivation study. *Can J Diabetes*. 2017;42(3):289–295. doi:10.1016/j.jcjd.2017.06.013
4. Katon WJ, Lin EH, Russo J, et al. Cardiac risk factors in patients with diabetes mellitus and major depression. *J Gen Intern Med*. 2004;19(12):1192–1199. doi:10.1111/j.1525-1497.2004.30405.x
5. Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of depression to diabetes types 1 and 2: epidemiology, biology, and treatment. *Biol Psychiatry*. 2003;54(3):317–329. doi:10.1016/S0006-3223(03)00569-9
6. Joynt KE, Whellan DJ, O'Connor CM. Depression and cardiovascular disease: mechanisms of interaction. *Biol Psychiatry*. 2003;54(3):248–261. doi:10.1016/S0006-3223(03)00568-7
7. Carney RM, Blumenthal JA, Freedland KE, et al. Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med*. 2005;165(13):1486–1491. doi:10.1001/archinte.165.13.1486
8. Carney RM, Freedland KE, Stein PK, et al. Heart rate variability and markers of inflammation and coagulation in depressed patients with coronary heart disease. *J Psychosom Res*. 2007;62(4):463–467. doi:10.1016/j.jpsychores.2006.12.004
9. Vaccarino V, Johnson BD, Sheps DS, et al. Depression, inflammation, and incident cardiovascular disease in women with suspected coronary ischemia: the National Heart, Lung, and Blood Institute-sponsored WISE study. *J Am Coll Cardiol*. 2007;50(21):2044–2050. doi:10.1016/j.jacc.2007.07.069
10. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord*. 2002;72(3):227–236. doi:10.1016/S0165-0327(01)00413-X
11. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442. doi:10.1371/journal.pmed.0030442
12. Teng PR, Yeh CJ, Lee MC, Lin HS, Lai TJ. Depressive symptoms as an independent risk factor for mortality in elderly persons: results of a national longitudinal study. *Aging Ment Health*. 2013;17(4):470–478. doi:10.1080/13607863.2012.747081
13. 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. doi:10.1016/j.genhosppsych.2013.01.006
14. Hofmann M, Kohler B, Leichsenring F, Kruse J. Depression as a risk factor for mortality in individuals with diabetes: a meta-analysis of prospective studies. *PLoS One*. 2013;8(11):e79809. doi:10.1371/journal.pone.0079809
15. van Dooren FE, Nefs G, Schram MT, Verhey FR, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2013;8(3):e57058. doi:10.1371/journal.pone.0057058

16. Pan A, Lucas M, Sun Q, et al. Increased mortality risk in women with depression and diabetes mellitus. *Arch Gen Psychiatry*. 2011;68(1):42–50. doi:10.1001/archgenpsychiatry.2010.176
17. Ting RZ, Lau ES, Ozaki R, et al. High risk for cardiovascular disease in Chinese type 2 diabetic patients with major depression--A 7-year prospective analysis of the Hong Kong Diabetes Registry. *J Affect Disord*. 2013;149(1–3):129–135. doi:10.1016/j.jad.2013.01.012
18. Chiu CJ, Wray LA, Ofstedal MB. Diabetes-related change in physical disability from midlife to older adulthood: evidence from 1996–2003 survey of health and living status of the elderly in Taiwan. *Diabetes Res Clin Pract*. 2011;91(3):413–423. doi:10.1016/j.diabres.2010.12.003
19. Cartierre N, Coulon N, Demerval R. Analyse confirmatoire de la version courte de la Center for Epidemiological Studies of Depression Scale (CES-D10) chez les adolescents [Confirmatory factor analysis of the short French version of the Center for Epidemiological Studies of Depression Scale (CES-D10) in adolescents]. *Encephale*. 2011;37(4):273–277. French. doi:10.1016/j.encep.2011.01.011
20. Egede LE, Nietert PJ, Zheng D. Depression and all-cause and coronary heart disease mortality among adults with and without diabetes. *Diabetes Care*. 2005;28(6):1339–1345. doi:10.2337/diacare.28.6.1339
21. Lotufo PA, Gaziano JM, Chae CU, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. *Arch Intern Med*. 2001;161(2):242–247. doi:10.1001/archinte.161.2.242
22. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. *J Am Coll Cardiol*. 2002;40(5):954–960. doi:10.1016/S0735-1097(02)02044-2
23. Saydah SH, Eberhardt MS, Loria CM, Brancati FL. Age and the burden of death attributable to diabetes in the United States. *Am J Epidemiol*. 2002;156(8):714–719. doi:10.1093/aje/kwf111
24. Lee TA, Shields AE, Vogeli C, et al. Mortality rate in veterans with multiple chronic conditions. *J Gen Intern Med*. 2007;22(Suppl 3):403–407. doi:10.1007/s11606-007-0277-2
25. Katon WJ. The comorbidity of diabetes mellitus and depression. *Am J Med*. 2008;121(11 Suppl 2):S8–15. doi:10.1016/j.amjmed.2008.09.008
26. McIntyre RS, Soczynska JK, Konarski JZ, et al. Should depressive syndromes be reclassified as “Metabolic Syndrome Type II”? *Ann Clin Psychiatry*. 2007;19(4):257–264. doi:10.1080/10401230701653377
27. Katon W, Russo J, Lin EH, et al. Depression and diabetes: factors associated with major depression at five-year follow-up. *Psychosomatics*. 2009;50(6):570–579. doi:10.1016/S0033-3182(09)70858-8
28. Mansur RB, Lee Y, Zhou AJ, et al. Determinants of cognitive function in individuals with type 2 diabetes mellitus: a meta-analysis. *Ann Clin Psychiatry*. 2018;30(1):38–50.
29. Goldstein BI, Carnethon MR, Matthews KA, et al. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2015;132(10):965–986. doi:10.1161/CIR.0000000000000022

## Neuropsychiatric Disease and Treatment

Dovepress

### Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the ‘PsycINFO’ database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>