

Increased Risk of Cardiovascular Disease and Mortality in Patients with Diabetes and Coexisting Depression: A Nationwide Population-Based Cohort Study

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Background: Previous studies have suggested that depression in patients with diabetes is associated with worse health outcomes. The aim of this study was to evaluate the risk of cardiovascular disease (CVD) and mortality in patients with diabetes with comorbid depression.

Methods: We examined the general health check-up data and claim database of the Korean National Health Insurance Service (NHIS) of 2,668,615 participants with type 2 diabetes mellitus who had examinations between 2009 and 2012. As NHIS database has been established since 2002, those who had been diagnosed with depression or CVD since 2002 were excluded. The 2,228,443 participants were classified into three groups according to the claim history of depression; normal group ($n=2,166,979$), transient depression group (one episode of depression, $n=42,124$) and persistent depression group (at least two episodes of depression, $n=19,340$). The development of CVD and mortality were analyzed from 2009 to 2017.

Results: Those with depression showed a significantly increased risk for stroke (transient depression group: hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.15 to 1.26) (persistent depression group: HR, 1.54; 95% CI, 1.46 to 1.63). Those with depression had an increased risk for myocardial infarction (transient depression group: HR, 1.25; 95% CI, 1.18 to 1.31) (persistent depression group: HR, 1.38; 95% CI, 1.29 to 1.49). The persistent depression group had an increased risk for all-cause mortality (HR, 1.66; 95% CI, 1.60 to 1.72).


Conclusion: Coexisting depression in patients with diabetes has a deleterious effect on the development of CVD and mortality. We suggest that more attention should be given to patients with diabetes who present with depressive symptoms.


Keywords: Cardiovascular diseases; Depression; Diabetes mellitus

INTRODUCTION

Diabetes is a chronic disease that has reached epidemic levels globally. According to the International Diabetes Federation,

diabetes is associated with an increased risk of developing cardiovascular disease (CVD), leading to a reduced life expectancy, higher healthcare expenditure, and a decreased quality of life [1]. Recently, the public health authority in Korea focused

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on mental health, particularly depression, as Korea had among the highest suicide rates of all the Organization for Economic Cooperation and Development (OECD) member countries for years [2]. Depression is the most common mental health condition in the general population [3], characterized by sadness, loss of interest or pleasure, feelings of low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration [4].

In recent years, many researchers have focused on the psychosocial aspects of diabetes and have suggested relationships between mental disorders and diabetes [5-8]. Several studies have suggested that depression in patients with diabetes is associated with worse health outcomes, due to poor adherence to treatment regimens [9-11], which leads to poor glycemic control and an increased risk for complications. However, only few studies have been conducted in a large population to evaluate the risk of CVD and mortality in patients with diabetes and comorbid depression. Past studies on depression in diabetes did not consider either the treatment duration for depression or recurrence of depression. The purpose of this study was to assess the risk of cardiovascular complications and mortality among subjects who have both diabetes and depression in the whole Korean population. We uniquely aimed to examine the difference in two depression groups according to their duration for depression.

METHODS

Source of data

This study analyzed data from the Korean National Health Insurance Service (NHIS) and claims database. The NHIS system is a mandatory health insurance program that covers 97.1% of the Korean population. In Korea, the NHIS is the single insurer, managed by the government. The NHIS includes an eligibility database (age, sex, socioeconomic variables, type of eligibility, household income level, etc.); a medical treatment claims database (based on medical bills that were claimed by medical service providers for their medical expenses); a health examination database (results of general health examinations and questionnaires on lifestyle and behavior); a medical care institution database (types of medical care institutions, location, equipment, and number of physicians); and death register. The NHIS database has been established since January 2002. We used the general health examination data and NHIS claims data including diagnoses, procedures, prescription records,

and mortality.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital of Korea (KBSMC 2019-09-012). Anonymous and deidentified information was used for analysis and; therefore, informed consent was not obtained.

Study population and exclusion criteria

Among the subjects of the general health check-up program, we selected 21,177,963 participants aged 30 years or older who had undergone a health examination between 2009 and 2012. If subjects had two or more examinations between 2009 and 2012, data from the first checkup was used in analysis. At baseline, 18,509,348 participants without type 2 diabetes mellitus (T2DM) were excluded. A diagnosis of T2DM was defined according to the following criteria: (1) by the presence of International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM) codes E11, E12, E13, or E14 and claims for at least one oral anti-diabetic agent or insulin at the baseline, or (2) fasting glucose level ≥ 126 mg/dL (obtained from the health examination database). Depression was defined by using the ICD-10-CM codes F32 and F33. Those with previously diagnosed depression between January 1st, 2002 and a year before the date of their first examination were excluded from the analysis ($n=177,995$). To avoid confounding by preexisting disease and minimize the possible effects of reverse causality, those diagnosed with CVD before the date of their examination were also excluded ($n=206,661$) (Supplementary Fig. 1). The development of CVD and death of participants were analyzed from the results of health check-up programs and claims database from January 1, 2009 to December 31, 2017 or until the date of death, whichever came first. We set a lag period of 1 year and excluded 26,168 participants to ensure that the diagnoses of stroke, myocardial infarction (MI) or death were newly made (Supplementary Fig. 2) [12].

Participants in national health check-up examinations provided written informed consent for the use of their data for research. All personal information was deleted, and only non-identifiable data were used for the analyses.

Definitions and measurements

Patients were considered to have T2DM if the ICD-10-CM codes E11-E14 were present and if there were claims for at least one oral anti-diabetic agent or insulin at baseline or a fasting glucose level ≥ 126 mg/dL. A diagnosis of depression was defined by the presence of ICD-10-CM codes F32-F33. The

endpoint of this study was the presence of newly diagnosed CVD or death. The cardiovascular complications comprised MI and stroke. MI was defined as hospitalization with the diagnostic codes of I21 and I22. Stroke was defined by the presence of ICD-10-CM codes I63 and I64, as well as a history of hospitalization with claims for brain magnetic resonance imaging or brain computed tomography.

The general health examination included history taking, blood pressure (BP), blood sampling after an overnight fast, urinalysis, and chest X-ray. The presence of hypertension was defined according to the presence of at least one claim per year for the prescription of anti-hypertensive agents, under ICD-10-CM codes I10–I15, or a systolic/diastolic BP $\geq 140/90$ mm Hg. The presence of dyslipidemia was defined according to the presence of at least one claim per year for the prescription of anti-hyperlipidemic agents under ICD-10 codes E78, or total cholesterol ≥ 240 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate < 60 mL/min [13]. Information on smoking and alcohol consumption was obtained using the questionnaires as mentioned above. In this study, heavy alcohol consumption was defined as intake ≥ 30 g/day. Regular exercise was defined as performing > 30 minutes of moderate physical activity at least five times per week, or > 20 minutes of strenuous physical activity at least three times per week. Income level was dichotomized at the lower 20th percentile.

Statistical analysis

Baseline characteristics are presented as mean with standard deviation or numbers and percentages. Clinical characteristics between the participants were compared using one-way analysis of variance for continuous variables, and the chi-square test for categorical variables. The incidence rates of stroke, MI, and death are presented per 1,000 person-years. Cox proportional hazards regression analysis was used to evaluate the association between the presence of depression and the incidence of stroke, MI, and death. The potential effects by age, sex, obesity, and CKD were evaluated using stratified analysis and interaction testing. The cumulative incidence probabilities of stroke, MI, and death were plotted using Kaplan-Meier curves. These results were expressed as hazard ratios (HRs) with 95% confidence interval (CI). Statistical significance was defined as two-sided P value < 0.05 . All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria; <http://www.Rproject.org>).

RESULTS

Baseline characteristics

The characteristics of participants at baseline are presented in Table 1. We identified 2,228,443 patients with T2DM at baseline. The participants were classified into three groups; those without depression (no depression [ND] group, $n = 2,166,979$), those with depression but without additional claims within 2 years after the date of claims for depression made (transient depression [TD] group, $n = 42,124$), and those with depression and repeated claims within 2 years (persistent depression [PD] group, $n = 19,340$). Patients in the depression groups tended to have more comorbidities such as CKD, hypertension, and dyslipidemia. Also, those in the depression groups had higher rates of prescription of insulin and multiple oral hypoglycemic agents, than those in the ND group. Additionally, patients in the depression groups tended to be physically inactive compared to those in the ND group.

Probability of stroke, MI, and all-cause mortality for up to 8 years according to claim history of depression

The Kaplan-Meier curves in Fig. 1 present the probability of stroke, MI, and death according to the history of depression. Patients in the PD and TD groups had a greater incidence of CVD than those in the ND group (log-rank $P < 0.001$). Having continuous claims data for depression was associated with increased all-cause mortality during the follow-up period compared to having no history of depression (log-rank $P < 0.001$). After up to 8 years of follow-up, the incidence of CVD, and all-cause mortality were associated with the number of claims for depression.

The risk of CVD and death among patients with T2DM with or without depression

Table 2 shows the results of the Cox proportional hazard regression analysis. The crude incidence rates of stroke were 5.5, 8.1, and 11.7 per 1,000 person-years in the ND, TD, and PD groups, respectively ($P < 0.001$); the crude incidence rates of MI were 3.5, 5.2, and 6.5 respectively. There was a positive relationship between the number of claims for depression treatment and the incidence of stroke, MI, and death. Both TD and PD groups showed a significantly increased risk for stroke (TD group: HR, 1.47; 95% CI, 1.40 to 1.54) (PD group: HR, 2.12; 95% CI, 2.01 to 2.24; $P < 0.001$) and risk for MI (TD group: HR, 1.51; 95% CI, 1.43 to 1.60) (PD group: HR, 1.88; 95% CI, 1.75

Table 1. Baseline characteristics of subjects according to the comorbidity of depression

Variable	ND (n=2,166,979)	TD (n=42,124)	PD (n=19,340)
Proportion, %	97.2	1.9	0.9
Male sex	1,358,838 (62.7)	18,125 (43.0)	7,236 (37.4)
Smoking status			
Never smoker	1,160,719 (53.6)	28,704 (68.1)	13,925 (72.0)
Former smoker	407,553 (18.8)	6,008 (14.3)	2,460 (12.7)
Current smoker	598,707 (27.6)	7,412 (17.6)	2,955 (15.3)
Alcohol drinking, g/day			
None	1,165,870 (53.8)	29,884 (70.9)	15,159 (78.4)
Mild (<30)	795,488 (36.7)	9,863 (23.4)	3,410 (17.6)
Heavy (≥30)	205,621 (9.5)	2,377 (5.6)	771 (4.0)
Exercise ^a	1,070,288 (49.4)	17,987 (42.7)	7,559 (39.1)
Income, lower 20%	476,661 (22.0)	9,895 (23.5)	4,755 (24.6)
CKD	212,160 (9.8)	5,859 (13.9)	3,455 (17.9)
Hypertension	1,171,049 (54.0)	25,584 (60.7)	12,814 (66.3)
Dyslipidemia	864,572 (39.9)	20,042 (47.6)	9,979 (51.6)
Antidiabetic agent ≥2 ^b	767,738 (35.4)	18,786 (44.6)	9,446 (48.8)
Use of insulin ^b	125,707 (5.8)	5,689 (13.5)	3,193 (16.5)
Treatment for diabetes ≥5 yr	631,998 (29.2)	15,121 (35.9)	8,009 (41.4)
Age, yr	56.5±11.8	61.0±11.1	63.3±10.6
BMI, kg/m ²	25.1±3.3	24.8±3.3	24.8±3.4
Total cholesterol, mg/dL	198.8±41.7	196.5±42.9	194.9±43.6
SBP, mm Hg	129.1±15.6	128.2±15.6	128.1±15.9
DBP, mm Hg	79.3±10.1	78.1±10.0	77.8±10.1
Fasting blood glucose, mg/dL	145.7±43.6	137.7±42.0	135.6±43.1
HDL-C, mg/dL	51.8±19.9	52.3±20.8	52.4±23.1
LDL-C, mg/dL	112.6±43.4	112.3±44.3	111.2±45.9
Triglyceride, mg/dL	151.9 (151.8–152.0)	143.8 (143.0–144.6)	142.4 (141.3–143.5)

Values are presented as number (%), mean ± standard deviation, or geometric means (range). *P* values were <0.0001 for all variables.

ND, no depression; TD, transient depression; PD, persistent depression; CKD, chronic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

^aRegular exercise was defined as performing >30 minutes of moderate physical activity at least 5 times per week or >20 minutes of strenuous physical activity at least 3 times per week, ^bWithin 1 year before the index date.

to 2.03; *P*<0.001) compared to the ND group (Table 2). The PD group had more than two-fold higher all-cause mortality (HR, 2.21; 95% CI, 2.13 to 2.30) compared to the ND group. After adjustment for confounding variables, the HRs were attenuated but showed consistently increased risks for CVD and death, with a 1.5-fold and 1.4-fold increased risk for stroke and MI, respectively, and a 1.7-fold increased risk for all-cause mortality compared to the ND group (Table 2).

Risk for CVD and mortality in subgroups

Risk for CVD and all-cause mortality was analyzed in various subgroups, setting the ND group as the reference after adjusting for all covariates (Supplementary Table 1). The associations between CVD and depression according to age, sex, BMI (cut off, 25.0 kg/m²), and use of insulin are shown in Fig. 2. Regarding the risk for stroke, we found significant interactions between depression and age. In the groups with depression, the risk for stroke was highest in subjects between 30 and 49-year-

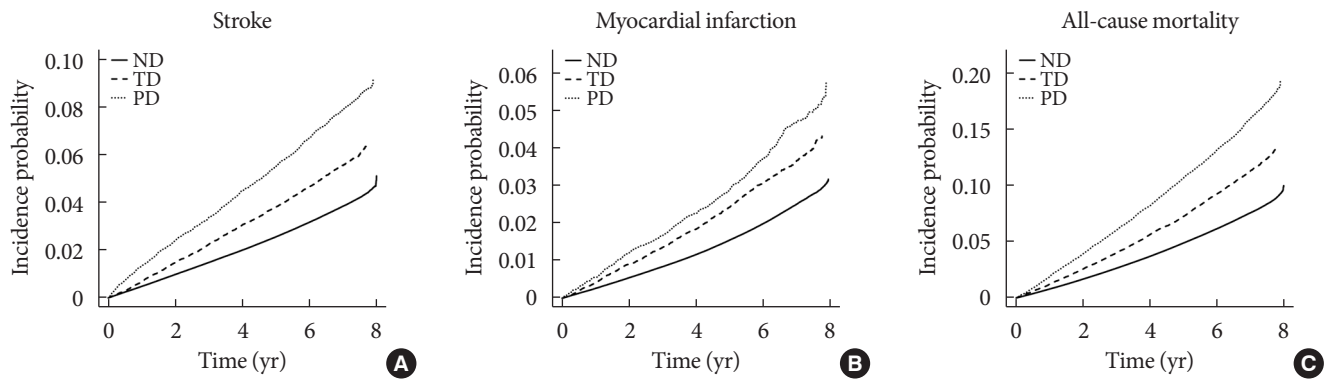


Fig. 1. Kaplan-Meier curves for the risk of cardiovascular disease and mortality according to status of depression. Kaplan-Meier curves were generated in order to visualize the cumulative incidence probability of (A) stroke, (B) myocardial infarction, and (C) all-cause mortality. ND, no depression; TD, transient depression; PD, persistent depression.

Table 2. HRs and 95% CIs of all-cause mortality, myocardial infarction and stroke by the status of comorbid depression

Variable	No. of event	Incidence rate, /1,000 person-yr	HR (95% CI)			
			Model 1	Model 2	Model 3	Model 4
Stroke						
ND	70,736	5.5	1 (reference)	1 (reference)	1 (reference)	1 (reference)
TD	1,990	8.1	1.47 (1.41–1.54)	1.29 (1.23–1.35)	1.28 (1.22–1.33)	1.20 (1.15–1.26)
PD	1,308	11.7	2.12 (2.01–2.24)	1.72 (1.62–1.81)	1.68 (1.59–1.78)	1.54 (1.46–1.63)
Myocardial infarction						
ND	44,688	3.5	1 (reference)	1 (reference)	1 (reference)	1 (reference)
TD	1,295	5.2	1.51 (1.43–1.60)	1.34 (1.27–1.42)	1.32 (1.25–1.40)	1.25 (1.18–1.32)
PD	743	6.5	1.88 (1.75–2.03)	1.56 (1.45–1.68)	1.51 (1.41–1.63)	1.38 (1.29–1.49)
All cause mortality						
ND	141,985	10.9	1 (reference)	1 (reference)	1 (reference)	1 (reference)
TD	4,151	16.5	1.52 (1.47–1.57)	1.42 (1.38–1.47)	1.39 (1.35–1.43)	1.27 (1.23–1.31)
PD	2,791	24.2	2.21 (2.13–2.30)	1.94 (1.87–2.01)	1.86 (1.80–1.93)	1.66 (1.60–1.72)

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for model 2+current smoking, alcohol and regular exercise; Model 4: adjusted for model 3+body mass index, hypertension, dyslipidemia, chronic kidney disease, fasting blood glucose, use of insulin, prescription of 2 or more antidiabetic agents.

HR, hazard ratio; CI, confidence interval; ND, no depression; TD, transient depression; PD, persistent depression.

old (HR, 1.38; 95% CI, 1.15 to 1.65; *P* for interaction=0.019). The overall effects of depression on risk estimates for CVD were consistent across the categories for subgroup analyses. However, there was no significant interaction between depression and subgroup variables with respect to the risk for MI (all *P* for interaction >0.05). There were interactions between depression and age, sex, and use of insulin in the analysis of all-cause mortality.

DISCUSSION

In this study, the participants with diabetes with comorbid depression showed a higher risk for development of cardiovascular complications and increased all-cause mortality compared to patients with diabetes without comorbid depression. Participants in the depression groups showed higher prescription rates of insulin and multiple oral anti-diabetic agents. When those with coexisting depression were stratified into two

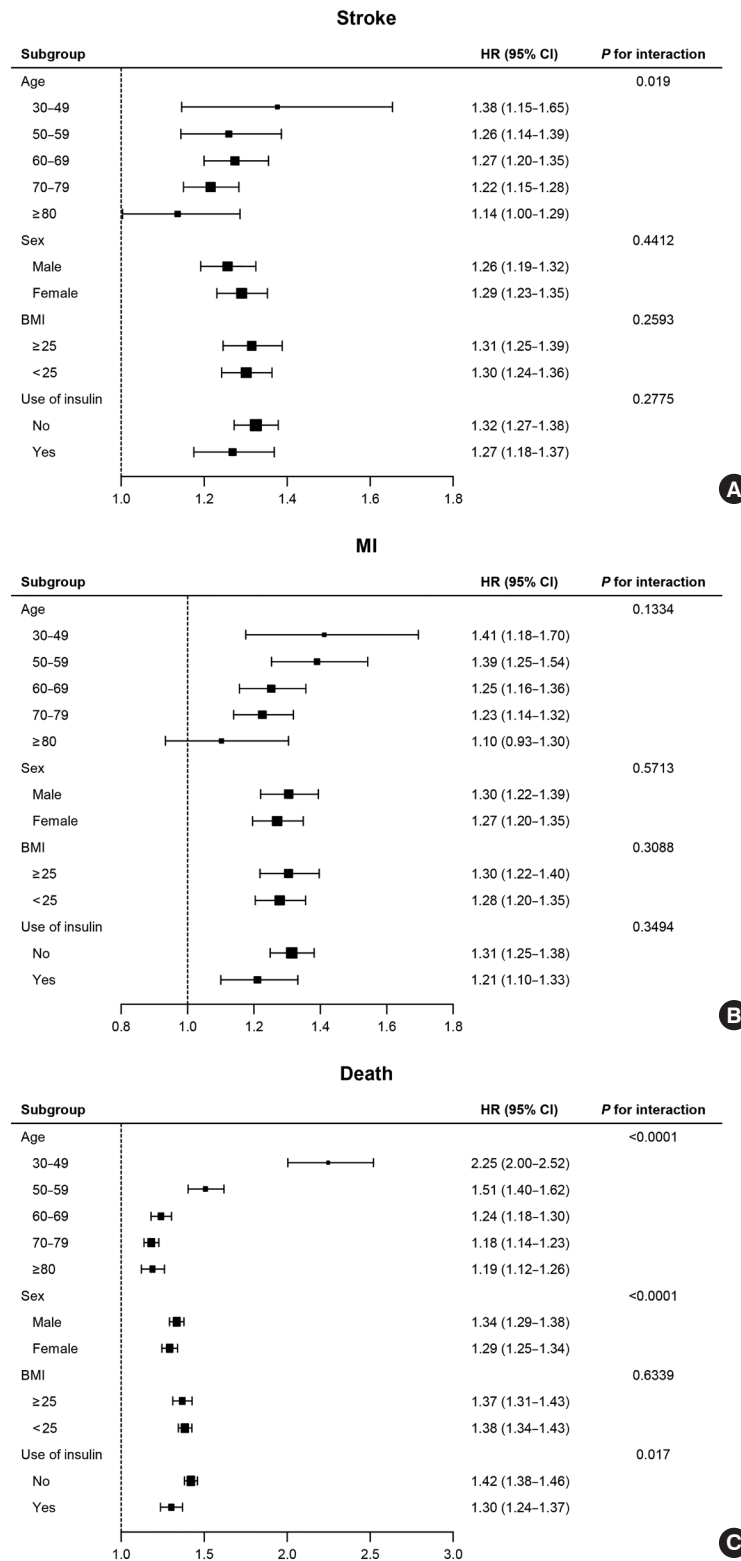


Fig. 2. Forest plots for risk of cardiovascular disease and mortality in subgroup analyses. (A) Risk of stroke, (B) risk of myocardial infarction (MI), and (C) risk of all-cause mortality. HR, hazard ratio; CI, confidence interval; BMI, body mass index.

groups according to their claims for depression treatment, subjects in the PD group showed a higher risk of CVD than those in the TD group. After adjusting for confounding variables, we consistently found an increased risk for CVD and all-cause mortality. In subgroup analyses, patients younger than 50 years showed a higher risk of stroke in the depression groups. However, we found no significant interactions between depression and the subgroups with the respect to the risk for MI.

Depression is frequently presented in the context of chronic medical conditions including diabetes mellitus [14]. The occurrence of depression is two to three times higher among patients with diabetes mellitus [15], and an increased prevalence of depression in patients with diabetes seems to be a global phenomenon [16-19]; this trend is also evident in South Korea. In our analysis using the Korean NHIS database, the prevalence of depression in Korean patients with diabetes was about two-fold higher compared to that in the general population [20].

Many studies reported that depression increases the risk of diabetes, and diabetes increases the risk of depression [21,22]. The mechanisms for explaining the relationship between depression and diabetes are unclear, but a bidirectional relationship is strongly suggested [23,24]. Previous studies have shown that individuals with diabetes and comorbid depression are at an increased risk for both micro- and macrovascular complications from diabetes and have higher mortality than those without depression [16,25]. As expected, we found an increased risk for CVD and all-cause mortality in patients with diabetes with comorbid depression compared to patients with diabetes without depression in this community-based cohort study. Our results are consistent with those of a longitudinal study in older Mexican-Americans [26]. In the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE) survey, the interaction between diabetes and depression was found to be synergistic, with higher mortality and a greater incidence of both macro- and microvascular complications [26]. In another large cohort study among veterans from the United States, participants with a double diagnosis (both T2DM and major depressive disorder [MDD]) were at an increased risk for MI compared to those without either condition [25]. However, their sample size was small and was not representative of the general population. A systematic review and meta-analysis including prospective studies also showed that depression was associated with a higher incidence of cardiovascular mortality [27]. However, many studies were mainly conducted in the United States and little is known about

Asian populations.

Although several studies have demonstrated the effects of comorbid depression on the development of CVD in patients with T2DM, only a limited number of studies have focused on the different effects of single episode of MDD versus recurrent MDD. Wagner et al. [28] reported that recurrent depression among postmenopausal women with T2DM was associated with vasoconstriction and endothelial dysfunction, but not among those who experienced a single episode of MDD. Our study assessed CVD outcomes among patients with T2DM with TD versus PD; our results highlight the importance of identifying individuals suffering from recurrent or prolonged depression.

Several hypothesis have been suggested in order to explain the unfavorable health outcomes in patients with diabetes and coexisting depression. First, behavioral changes accompanied by mood disorders might worsen glycemic control [29,30]. Depressive symptoms are associated with unhealthy behaviors (i.e., eating disorders with increased caloric intake, lower levels of physical activities, and smoking) that result in suboptimal glycemic control. Individuals with diabetes and comorbid major depression have higher odds of functional disability compared to individuals with either diabetes or depression alone [31]. Poor compliance to diabetes treatment and unhealthy behaviors might be associated with unfavorable glycemic control as well as an increased risk of cardiovascular complications. Interestingly, in our study, the proportion of current smokers and alcohol drinkers at baseline were lower in the depression groups. The fasting blood glucose (FBG) level and BMI at baseline in the depression groups were lower than those without depression. To date, a number of studies have found that association between depression and hyperglycemia in T2DM patients is not significant, while several studies have shown that depression and depressive symptoms are associated with poor glucose control. When examined meta-analytically, the association between poor glucose control and depression has been found to be more significant in type 1 diabetes mellitus as compared to T2DM [32]. Depression is also associated with increased risk of hypoglycemia. Biologic changes in depression such as dysregulation of autonomic dysfunction and increased inflammatory factors could lead to fluctuations in glycemic control [33]. Suboptimal glycemic control may account for some of the relationship between depression and increased risk of CVD and mortality, but it seems there are other unknown mechanisms on this relationship. As we have not evalu-

ated the behavioral changes and did not measure HbA1c in this study, more tailored studies are needed to understand the mechanisms between glycemic control and CVD in depressed patients. Another possible explanation is the direct effects of antidepressants on FBG levels. A variety of studies have reported either hypoglycemic or euglycemic effects of selective serotonin reuptake inhibitor medication [34]. As we could not obtain the study participants' detailed information about antidepressants, further studies are needed to assess the effects of antidepressants in diabetics with comorbid depression. Despite of some ambiguous result in our study, the increased risk of CVD and mortality in the depression groups were consistently observed after adjusting for covariates including smoking, alcohol consumption, FBG, and BMI.

There are several potential biological mechanisms by which depression may interact with the mechanisms of diabetes and result in deterioration of glycemic control, resulting in adverse health outcomes. Previous studies have suggested that dysregulation of the hypothalamus-pituitary-adrenal axis, alterations in the sympathetic nervous system, and a pro-inflammatory state play a role in the pathophysiology of both depression and diabetes [15,35]. Additionally, both depression and diabetes have been shown to be associated with increased platelet adhesiveness or aggregation, increased inflammatory markers, and endothelial dysfunction [10]. These biological changes in depression and diabetes may partially contribute to the development of CVD and higher mortality.

Regarding the risk for stroke, we found significant interactions between depression and age. Among participants aged between 30 and 49 years, those with comorbid depression showed an increased risk for stroke than older participants. Moreover, this group (aged 30 to 49 years) presented higher mortality from any cause (HR, 2.25; 95% CI, 2.00 to 2.52; *P* for interaction <0.001). These results are in line with previous studies. The American Heart Association statement demonstrated that MDD and bipolar disorder predispose youth to accelerated atherosclerosis and early CVD [36]. Therefore, early detection and proper management for the first episode of depression, especially in younger patients with T2DM, is important. As observed in our results, there is greater mortality among men suffering from depression compared to women with PD (HR 1.59, 95% CI 1.51–1.67, *P* for interaction <0.001). Similar results were also found in a Danish cohort [37], where patients with unipolar depression showed excess mortality and reduced life expectancy compared to the general population,

particularly among men and younger individuals. The meta-analysis suggests that diabetes can significantly increase the risk of suicide [38]. Previous cross-sectional study in Korea demonstrated that comorbid diabetes and depression was associated with a substantial increase in the risk of suicidal ideation [39]. In our findings, it remains unclear whether the higher mortality associated with depression can be attributed to unnatural causes (e.g., suicide) or natural causes (e.g., stroke or MI) but our results imply that history of depression is an important indicator of increased mortality including suicide. There was no interaction between obesity and the risk of CVD and mortality. We also found no interaction between insulin treatment and the risk of stroke or MI. However, there was a significant interaction between insulin treatment and all-cause mortality (*P* for interaction=0.017). The biologic and behavioral mechanisms that link depression with adverse health outcomes are still unclear. But depression might be associated with delayed intensification of treatment; for example, delayed initiation of insulin therapy. Many people with depression find it difficult to make decisions and have poor self-esteem, these depressive symptoms could contribute to a delay in initiation of insulin therapy [40].

Our findings support the hypothesis that diabetes and coexisting depression have unfavorable effects on various health outcomes. However, our study has several limitations. First, this study was an observational study using claims data from the Korean NHIS database. Findings from this study may not be generalized to other ethnic groups. Also, it did not include institutionalized individuals with severe depression or those with other serious medical illnesses who might have missed their biennial health examination. In Asian countries including South Korea, people with depressive symptoms are less likely to visit mental health specialists due to the stigma of mental illness. The presence of depression in this study was calculated based on the diagnostic codes from the claims data. This method might have caused misclassification of study subjects and underestimation of the depression population in our study. Also, as the NHIS database has been established since January 2002, we could not collect previous history of depression or CVD beyond the time frame of our study. Second, clinical information was not available from the database. We could not collect detailed information about patients' quality of life, severity of their depressive symptoms, or disabilities in their daily life. We also did not assess the behavioral changes including medication adherence, smoking habits, or alcohol con-

sumption after the diagnosis of depression during the follow-up period. In addition, we could not obtain laboratory data such as HbA1c to assess their adherence to diabetes treatment regimens in this study. A lack of physiologic markers of inflammation and autonomic nervous systems is also a limitation of our study. This study also did not consider the effects of medication, which might have potential effects on the development of cardiovascular complications. There is a systematic review demonstrated that antidepressants were not associated with an increased mortality rate and not associated with adverse cardiovascular outcomes [41]. Regarding cardiovascular efficacy and safety of antidiabetic drugs, UKPDS demonstrated that metformin reduced the risk of fatal macrovascular complications compared with other modalities. UKPDS group also demonstrated that treatment with SUs showed a trend toward protection against MI rather than augmentation of cardiovascular mortality. We were unable to assess the individuals' prescribed antidiabetic drugs, however, according to Ko et al. [42], metformin has been the most commonly used antidiabetic drug in Korea (80.4% in 2013), and sulfonylurea remained the most commonly prescribed second-line agents. Lastly, the causes of death of the participants were not clear in this study. Future studies regarding the effects of comorbid depression in patients with diabetes should evaluate the cause-specific mortality.

Despite these limitations, our study has several strengths. First, this is a large-scale national population cohort study of patients with T2DM that evaluated the influence of newly diagnosed depression on the development of CVD and mortality. Second, we classified study subjects with depression into two groups using their claims data during the follow-up period. Past studies on depression in diabetes did not consider either the duration for depression or recurrence of depression. Therefore, we sought to determine whether the patients with prolonged treatment for depression have higher risk for CVD and mortality than patients who required short term treatment for depression. In this study, we did not use self-reported questionnaires for depressive symptoms. Actual claims data for depression treatment may reflect their treatment response or depression severity. Third, we performed subgroup analyses in order to evaluate the potential effects by age, sex, obesity, and use of insulin. Our findings reflect the current status of depression and T2DM on a nationwide scale in Korea. The result of this study may serve as a basis for developing an effective guideline for screening and treating depression in patients with

T2DM.

In conclusion, this study suggests that the coexisting depression in patients with diabetes has a deleterious effect on the development of CVD and mortality. Importantly, patients with diabetes were significantly less likely to seek consultation for their depressive symptoms, whereas those with other chronic diseases, such as hypertension, had higher consultation rates [43]. Therefore, clinicians should give more attention to mental health among patients with T2DM in addition to their physical health problems. Further investigation is required to explain whether effective interventions for depression would improve cardiovascular outcomes and mortality in patients with diabetes.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at <https://doi.org/10.4093/dmj.2020.0008>.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: I.J.

Acquisition, analysis, or interpretation of data: H.K., S.E.P., K.D.H., Y.G.P., Y.H.K.

Drafting the work or revising: I.J., H.K., S.E.P.

Final approval of the manuscript: I.J., H.K., S.E.P., K.D.H., Y.G.P., Y.H.K., E.J.R., W.Y.L.

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