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Association between antidepressants and the risk of diabetic foot ulcers and amputation in antidepressant-naïve type 2 diabetes mellitus patients: A nested case-control study

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ABSTRACT

Aims: Antidepressants are widely used by individuals with type 2 diabetes mellitus (T2DM). This study aimed to explore the correlation between antidepressant use, considering specific antidepressant subclasses or cumulative doses, and diabetic foot ulcer (DFU) risk.
Methods: This nested case-control study was conducted using a representative population-based Korean cohort database from 2002 to 2019. Participants with DFUs were matched with participants without DFUs based on age, sex, date of T2DM diagnosis, and follow-up duration. In total, 791 DFUs and 3900 controls were included. The association between antidepressant use or cumulative dose of each antidepressant subclass, DFU risk and amputation risk was examined using a conditional logistic regression model.
Results: Antidepressant ever-use was associated with an increased incidence of DFUs compared with non-use. Furthermore, an increase in DFU risk was evident with increasing cumulative antidepressant dosage, particularly among tricyclic antidepressant (TCA) ever-users and selective serotonin reuptake inhibitors (SSRIs) ever-users. Additionally, antidepressant ever-users displayed a higher risk of DFUs requiring amputation, which was consistently observed when the cumulative dosages of overall antidepressants and TCAs were considered.
Conclusion: Caution is advised when administering TCAs and SSRIs in antidepressant-naïve T2DM patients to reduce DFU and the consequent amputation risk.

1. Introduction

Antidepressant use in individuals with type 2 diabetes mellitus (T2DM) who have not previously used antidepressants is frequently employed across various clinical aspects, including the management of neuropathic pain and the treatment of comorbid psychiatric conditions such as depression. The prevalence of depression among T2DM patients is substantial and exhibits a bidirectional relationship [1–4]. Furthermore, depression has been associated with detrimental effects on T2DM management, including medication adherence and complication development [5–7]. Notably, the administration of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), to T2DM patients with coexisting depression has demonstrated improvements in both depressive symptoms and glycemic control [8]. Given these considerations, a *meta*-analysis conducted in 2021 determined that the prevalence of antidepressant prescriptions among T2DM patients exhibiting depressive symptoms was approximately 29 % [9], and the incidence rate of antidepressant use showed a 2.4-fold increase following the initiation of T2DM treatment [10]. Additionally, severe psychological distress and other psychiatric disorders, such as sleep disorders, generalized anxiety disorder, specific phobias, and panic disorder, all of which are indications for antidepressant interventions, are associated with T2DM [11–13]. Concurrently, specific classes of antidepressants, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake

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inhibitors (SNRIs), have been firmly established as treatment modalities for diabetic neuropathy [14]. Furthermore, bupropion, a norepinephrine-dopamine reuptake inhibitor, is effective in managing neuropathic pain, whereas SSRIs may serve as alternative options for chronic pain [15].

Diabetic foot ulcers (DFUs) are a multifaceted and end-stage complication of DM arising from a combination of peripheral artery disease and motor, sensory, and autonomic neuropathy, often triggered by repetitive or excessive stress and infection [16–18]. Given its prevalence and unfavorable outcomes, the burden of DFU contributes significantly to major health concerns. In 2021, the International Diabetes Federation reported a global population of 537 million adults with DM, and it was estimated that 18.6 million of them could potentially develop DFUs [19,20], and the lifetime prevalence of DFUs may be as high as 25 % [21]. Additionally, DFUs are closely linked to lower-extremity amputations, diminished quality of life, and elevated mortality rates [22–24]. DFUs exhibit a considerable recurrence rate, with approximately 40 % of cases recurring within one year and 65 % recurring within five years [16]. However, there are limited studies investigating the association between the initiation of antidepressant therapy or the cumulative dose of antidepressant subclasses in T2DM patients and the subsequent risk of DFUs. Only one longitudinal study showed that using antidepressants, without focusing on the cumulative dose, in T2DM patients with depression was not associated with T2DM microvascular complications, including DFUs [25].

Numerous interventions aimed at preventing DFUs and other related complications exist, encompassing lifestyle modifications, education on diabetic care, glycemic control, and smoking cessation [21,26]. However, the evidence supporting the effectiveness of these measures for primary prevention remains limited [27,28]. Consequently, avoidance of medications that could potentially elevate the DFU risk might serve as a criterion for selecting initial antidepressants among patients with T2DM who have not previously used antidepressants. In this study, we sought to establish a connection between the use of antidepressants and the subsequent risk of DFUs in patients with T2DM by comparing those using antidepressants to T2DM patients who had not previously used antidepressants. Our focus was on the specific types of antidepressants (including SSRIs, SNRIs, TCAs, mirtazapine, bupropion, trazodone, and tianeptine) and the cumulative dosage of antidepressants administered following the diagnosis of T2DM.

2. Subjects, materials and methods

2.1. Data source

We utilized the Korea National Health Insurance Service-National Sample Cohort (NHIS-NSC) database, a nationwide, representative population-based repository of prospectively collected data in South Korea, covering January 1, 2002, to December 31, 2019 [29]. The Korea National Health Insurance (NHI) is a single insurer that, along with the participation of all healthcare providers and citizens in Korea, provides universal healthcare coverage. The study cohort comprised 1,024,340 participants, equivalent to 2.2 % of the population living in Korea, by systematic stratified random sampling with proportional allocation. The NHIS-NSC database encompasses a range of sociodemographic variables, health insurance classifications (including National Health Insurance and Medical Aid Program), mortality records, diagnostic information, and prescribed medications. All participants were tracked until 2019, barring instances of NHI disqualification (including emigration) or death.

The research protocol received approval from the Institutional Review Board (IRB) at Severance Hospital in Seoul, Republic of Korea (IRB No: [4–2023–0942]). The IRB waived the requirement for written informed consent, as the investigators solely accessed the database for academic purposes, without utilizing any personally identifiable information.

2.2. Study design and participants

We conducted a nested case-control study. A total of 99,025 participants diagnosed with T2DM who were prescribed antihyperglycemic medication for at least 90 days (excluding participants who might have been misdiagnosed or had symptoms too mild to warrant medication use, as well as those with illegal proxy prescriptions) were included. Patients were excluded if they were younger than 40 years of age, were T2DM-free after enrollment in the cohort for less than one year (one year wash out period), and were beneficiaries of the Medical Aid Program prior to T2DM diagnosis. Participants eligible for the study were followed-up from the first date of their T2DM diagnosis until the earliest occurrence of a DFU diagnosis, disqualification from the NHI, death, or conclusion of the observation period (December 31, 2019).

Patients were diagnosed with DFUs (T2DM with diabetic foot ulcers, T2DM with diabetic foot ulcers and gangrene, T2DM with other and unspecified diabetic foot complications) were identified and the cases for this study were selected based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). The index date, 180 days before the first DFU diagnosis date, was chosen to account for the potential delayed effects of antidepressants and the chronicity of DFU pathogenesis [30,31]. Follow-up duration encompassed the period from the date of T2DM diagnosis to the date of DFU diagnosis.

The controls were defined as participants who did not receive a DFU diagnosis during the follow-up period. Each case was matched with controls selected from a pool of eligible cohort participants with replacement, and the cases were used as their own controls. Matching of controls was executed based on the attributes of the corresponding cases, including age (within ± one year), sex (male or female), the date of the first T2DM diagnosis (within ± 30 days), and the duration of follow-up among participants who were at risk of DFU diagnosis at the time of case selection. The controls shared the same index date of their matched cases.

For both cases and controls, we implemented the following exclusion criteria: (1) Follow-up duration of fewer than two years (accounting for the time from the diagnosis of DFUs following T2DM diagnosis [32–34]); (2) No prescription for antihyperglycemic medication that lasted for at least 90 days before index date (to consider the effect of antihyperglycemic medication on the DFU risk); (3) Any history of antidepressant prescription before the diagnosis of T2DM, regardless of the reason for the prescription (in order to conduct analysis among antidepressant-naïve T2DM patients); (4) Undergoing a lower-extremity amputation procedure before the T2DM diagnosis; (5) Presence of missing data regarding living region and income level. After exclusion, controls were randomly selected from the matched control group at a ratio of 1:5, and controls without matched cases were excluded. A total of 791 cases and 3900 controls were included in the analyses. Of the 791 cases, five were matched at a 1:1 ratio, four at a 1:2 ratio, five at a 1:3 ratio, and thirteen at a 1:4 ratio.

2.3. Exposure

The exposure under investigation was the use of antidepressants that are approved and licensed in Korea. The study encompassed seven categories of antidepressants: SSRIs, including Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, and Vortioxetine; SNRIs such as Desvenlafaxine, Duloxetine, Milnacipran, and Venlafaxine; TCAs, including amitriptyline, clomipramine, doxepin, and imipramine; mirtazapine; trazodone; bupropion; and tianeptine. To quantify exposure, cumulative dose calculations were based on the cumulative defined daily doses (cDDD) as established by the World Health Organization (WHO). The cDDD was computed for all subclasses and each specific subclass of antidepressants, considering prescriptions provided during both outpatient visits and hospital admissions from the initial prescription date to the index date. In alignment with the delayed-effect

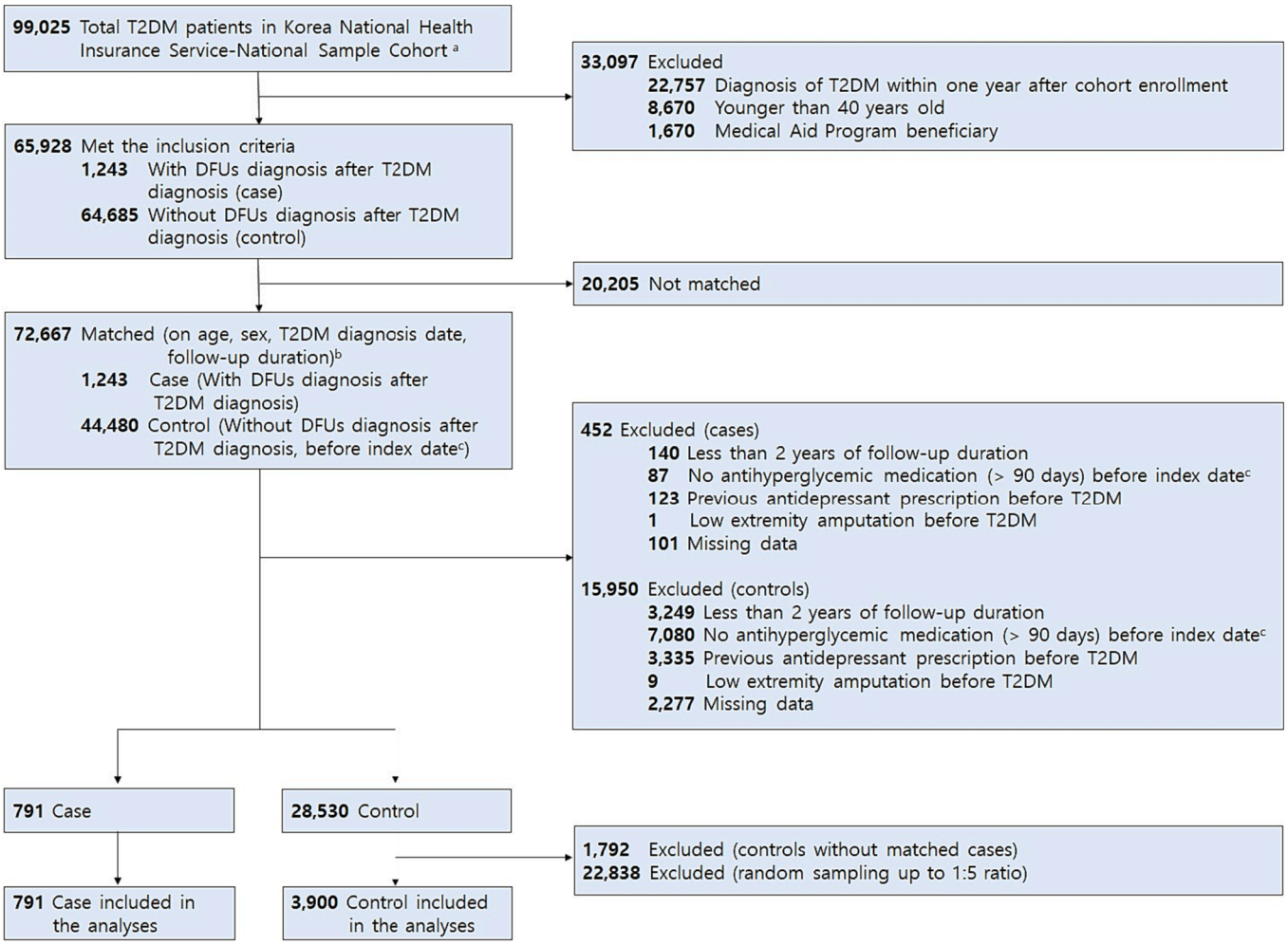

Fig. 1. Flow diagram of the study participants selection in the nested case-control study Abbreviation: T2DM, Type 2 Diabetes Mellitus; DFU, Diabetic Foot Ulcer a Korea National Health Insurance Service-National Sample Cohort (NHIS-NSC) database is a longitudinal cohort with 1,024,340 participants from January 1, 2002, to December 31, 2019. The NHIS-NSC database encompasses a range of sociodemographic variables, health insurance classifications, mortality records, diagnostic information, prescribed medications. b Age (within ±one year), sex (male or female), the date of the first T2DM diagnosis (within ±30 days), and the duration of follow-up.

characteristics observed in antidepressant use and in accordance with antidepressant usage guidelines in the United States and Korea [35,36], a threshold of 30 cDDDs was selected to represent the least significant prescription level. The mean cumulative dose for each antidepressant subclass is shown in Supplementary Table 1. The "ever-use" group of antidepressants was defined as individuals who had taken any subclass of antidepressant exceeding the threshold of the least significant prescription level (30 cDDDs).

2.4. Covariates

Two socioeconomic characteristics based on the index date, area of residence (capital area, metropolitan area, and province) and economic status (subdivided by the premium amount of NHI: low, middle, and high), were used as covariates. Diagnoses prior to the index date, such as hypertension, myocardial infarction, heart failure, cerebrovascular disease, chronic renal disease, chronic liver disease, cancer, and any psychiatric disease, were included. Specific diagnoses of psychiatric diseases were not incorporated because data masking was implemented for privacy protection. To adjust for T2DM severity, we included T2DM-related complications, such as diabetic neuropathy, angiopathy, retinopathy, and nephropathy, and hemodialysis. The types of antihyperglycemic medications used for at least 90 days during the follow-up period were as follows: Biguanides, DPP-4 inhibitors, SGLT2 inhibitors, Thiazolidinediones, Sulfonylureas, Meglitinides, Alpha-glucosidase inhibitors, and insulin. The types of antihypertensive medications that lasted for at least 90 days during the follow-up period included calcium channel blockers, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, thiazides, and alpha blockers. Other medications used as covariates included statins (prescribed for >90 days during the follow-up period), antiplatelet agents (prescribed for more than 90 days during follow-up period, including aspirin, clopidogrel, ticlopidine, and cilostazol), first-generation antipsychotics (prescribed for >30 days during the follow-up period), and second-generation antipsychotics (prescribed for >30 days during the follow-up period). All ICD-10 diagnostic codes and major ingredient codes of the medications used in the analyses are provided in Supplementary Table 2.

2.5. Statistical analysis

To investigate the potential association between antidepressant use and DFUs, a conditional logistic regression model was used. Given that the cases were considered their own controls, the calculated odds ratios from conditional logistic regression served as unbiased estimators of the hazard ratio and were thus presented as incidence rate ratios (IRs)

Table 1
Baseline characteristics of diabetic foot ulcer cases and matched controls.

Variables	Case		Control		Crude			
	n	(%)	n	(%)	IR	95% CI		
Total	791	(16.9)	3900	(83.1)				
Age at the index date[a]								
40–49	41	(5.2)	210	(5.4)	-			
50–59	210	(26.5)	1052	(27.0)	-			
60–69	244	(30.8)	1241	(31.8)	-			
70–79	223	(28.2)	1088	(27.9)	-			
more than 80	73	(9.2)	309	(7.9)	-			
Sex[a]								
Male	538	(68.0)	2660	(68.2)	-			
Female	253	(32.0)	1240	(31.8)	-			
Area of residence								
Capital area	303	(38.3)	1653	(42.4)	1.000			
Metropolitan	223	(28.2)	938	(24.1)	**1.299**	**1.070**	-	**1.578**
Province (rural)	265	(33.5)	1309	(33.6)	1.088	0.907	-	1.306
Economic status[b]								
Low	172	(21.7)	638	(16.4)	**1.339**	**1.082**	-	**1.655**
Middle	311	(39.3)	1537	(39.4)	1.000			
High	308	(38.9)	1725	(44.2)	0.870	0.729	-	1.039
Comorbidity[c]								
Psychiatric disorder	349	(44.1)	1672	(42.9)	1.044	0.887	-	1.229
Hypertension	636	(80.4)	3087	(79.2)	1.075	0.879	-	1.314
Myocardial infarction	65	(8.2)	190	(4.9)	**1.771**	**1.315**	-	**2.384**
Heart failure	146	(18.5)	557	(14.3)	**1.367**	**1.106**	-	**1.689**
Cerebrovascular disease	259	(32.7)	1055	(27.1)	**1.351**	**1.134**	-	**1.608**
Chronic renal disease	104	(13.1)	164	(4.2)	**3.748**	**2.844**	-	**4.939**
Chronic liver disease	13	(1.6)	66	(1.7)	0.981	0.536	-	1.798
Cancer	12	(1.5)	87	(2.2)	0.676	0.365	-	1.251
T2DM severity[c]								
Diabetic nephropathy	193	(24.4)	679	(17.4)	**1.573**	**1.302**	-	**1.899**
Hemodialysis	17	(2.1)	9	(0.2)	**12.780**	**5.005**	-	**32.635**
Diabetic neuropathy	430	(54.4)	1321	(33.9)	**2.588**	**2.191**	-	**3.058**
Diabetic angiopathy	391	(49.4)	1294	(33.2)	**2.134**	**1.809**	-	**2.516**
Diabetic retinopathy	336	(42.5)	1215	(31.2)	**1.714**	**1.457**	-	**2.015**
Type of antihyperglycemic medication[c,d]								
Biguanides	693	(87.6)	3380	(86.7)	1.122	0.883	-	1.425
DPP-4 inhibitors	338	(42.7)	1460	(37.4)	**1.318**	**1.105**	-	**1.571**
SGLT2 inhibitors	19	(2.4)	96	(2.5)	0.967	0.575	-	1.625
Thiazolidinediones	173	(21.9)	699	(17.9)	**1.318**	**1.086**	-	**1.598**
Sulfonylureas	640	(80.9)	2893	(74.2)	**1.537**	**1.259**	-	**1.877**
Meglitinides	90	(11.4)	220	(5.6)	**2.275**	**1.738**	-	**2.977**
Alpha-glucosidase inhibitors	280	(35.4)	895	(22.9)	**1.998**	**1.678**	-	**2.381**
Insulin	91	(11.5)	120	(3.1)	**4.795**	**3.514**	-	**6.544**
Type of antihypertensive medication[c,d]								
Calcium channel blocker	434	(54.9)	2039	(52.3)	1.110	0.946	-	1.303
Beta blocker	277	(35.0)	1191	(30.5)	**1.226**	**1.038**	-	**1.449**
Angiotensin Converting-enzyme inhibitor	163	(20.6)	660	(16.9)	**1.301**	**1.065**	-	**1.588**
Angiotensin Receptor blocker	504	(63.7)	2255	(57.8)	**1.294**	**1.098**	-	**1.525**
Thiazide	352	(44.5)	1602	(41.1)	1.153	0.981	-	1.354
Alpha blocker	73	(9.2)	306	(7.8)	1.214	0.910	-	1.620
Other medication[c]								
Statin[d]	490	(61.9)	2402	(61.6)	1.035	0.877	-	1.220
Antiplatelet agent[d,e]	498	(63.0)	2120	(54.4)	**1.471**	**1.245**	-	**1.739**
First generation antipsychotics[f]	9	(1.1)	31	(0.8)	1.409	0.666	-	2.979
Second generation antipsychotics[f]	22	(2.8)	55	(1.4)	**2.057**	**1.230**	-	**3.441**

Abbreviation: **Bold**, statistically significant; IR, incidence rate ratio; CI, confidence interval; T2DM, Type 2 Diabetes Mellitus; DPP-4, Dipeptidylpeptidase-4; SGLT2, Sodium Glucose Co-Transporter 2;
a No crude incidence rate ratio was calculated due to its use in the matching process.
b Divided by the premium amount of National Health Insurance. The lowest three deciles were 'low' group, while the highest three deciles were 'high' group. The remaining deciles were classified as the 'middle' group.
c More details in Supplementary Table 2.
d Prescribed for more than 90 days during follow-up period.

e Including aspirin, clopidogrel, ticlopidine, and cilostazol.
f Prescribed for more than 30 days during follow-up period.

Table 2
Relationship between antidepressant use or cumulative dose and risk of diabetic foot ulcers.

Variables	Case (n = 791)		Control (n = 3900)		Diabetic foot ulcers								
	n	(%)	n	(%)	Crude IR	95% CI			p-for-trend	Adjusted IR[a]	95% CI		p-for-trend
Antidepressant use													
Never use[b]	618	(78.13)	3424	(87.79)	1.000					1.000			
Ever use	173	(21.87)	476	(12.21)	**2.171**	**1.767**	-	**2.667**		**1.620**	**1.267**	- **2.071**	
Cumulative dose (antidepressant)									**<0.0001**				**0.0005**
30-60 cDDDs	42	(24.28)	110	(23.11)	**2.269**	**1.545**	-	**3.332**		**1.793**	**1.169**	- **2.750**	
60-180 cDDDs	44	(25.43)	155	(32.56)	**1.653**	**1.160**	-	**2.356**		1.368	0.923	- 2.027	
180-365 cDDDs	34	(19.65)	86	(18.07)	**2.385**	**1.567**	-	**3.629**		**1.659**	**1.037**	- **2.653**	
> 365 cDDDs	53	(30.64)	125	(26.26)	**2.682**	**1.880**	-	**3.825**		**1.811**	**1.179**	- **2.781**	
Cumulative dose (antidepressant)									**<0.0001**				**0.0009**
Q1 (30-62.33 cDDDs)	46	(26.59)	117	(24.58)	**2.320**	**1.618**	-	**3.384**		**1.803**	**1.192**	- **2.726**	
Q2 (62.33-143.5 cDDDs)	36	(20.81)	125	(26.26)	**1.662**	**1.126**	-	**2.455**		1.436	0.935	- 2.206	
Q3 (143.5-361.13 cDDDs)	42	(24.28)	120	(25.21)	**2.118**	**1.454**	-	**3.086**		**1.539**	**1.009**	- **2.384**	
Q4 (> 361.13 cDDDs)	49	(28.32)	114	(23.95)	**2.722**	**1.884**	-	**3.933**		**1.753**	**1.122**	- **2.739**	

Abbreviation: **Bold**, statistically significant IR, incidence rate ratio; CI, confidence interval; cDDD, cumulative defined daily dose; Q, quartile.
a Adjusted for area of residence, economic status, past diagnosis prior to the index date (hypertension, myocardial infarction, heart failure, cerebrovascular disease, chronic renal disease, chronic liver disease, cancer, any psychiatric diseases), T2DM-related complications (diabetic neuropathy, diabetic angiopathy, diabetic retinopathy, diabetic nephropathy, and hemodialysis), type of antihyperglycemic medication (biguanides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and insulin), type of antihypertensive medication (calcium channel blockers, beta blockers, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, thiazides, and alpha blockers), statins, antiplatelet agents (including aspirin, clopidogrel, ticlopidine, and cilostazol), first generation antipsychotics, and second generation antipsychotics.
b All subclasses of antidepressant were prescribed lower than the threshold of the least significant prescription level (30 cDDDs).

[37–39]. Crude IRs with 95 % confidence intervals (CI), adjusted IRs (adjusted for all covariates and whether each antidepressant subclass was used or not) with 95 % CI, and p-value for trend (in the analysis based on cumulative dose) were calculated. Subgroup analyses were conducted based on age categories (Individuals below their 50 s, those in their 60 s, and those aged 70 and above) as well as sex (male and female). In addition, the risk of DFUs leading to amputation, irrespective of the reasons for amputation, was examined following a diagnosis of T2DM. Additionally, sensitivity analyses were conducted, incorporating alternative index dates (DFU diagnosis date, 30 days prior to DFU diagnosis date, and 365 days prior to DFU diagnosis date), varying exclusion criteria for the minimum duration between DM diagnosis date and DFU diagnosis date (follow-up duration of less than five years), and adopting different cDDD thresholds for the least significant prescription level (14 cDDDs and 60 cDDDs). The assumptions for conditional logistic regression were satisfied, including the absence of multicollinearity, as indicated by variance inflation factors (VIF) all being less than 1.86. For all analyses, SAS software (SAS Institute; Version 9.4) was performed and two-tailed P-value 0.05 or less was used as statistical significance.

3. Results

The inclusion criteria were fulfilled by a total of 4,692 participants, comprising 791 cases and 3,900 controls (Fig. 1). The mean follow-up period (from the date of T2DM diagnosis to DFU diagnosis) for cases was 9.17 years (standard deviation, SD: 3.60 years), while for controls it was 9.18 years (SD: 3.60 years). Table 1 shows baseline characteristics of the participants and crude IR of each variable. Most participants were in the age range of 50 to 79 years (86.3 %), and male gender was more prevalent (68.2 %). About 32.4 % of participants resided in rural areas, while 39.2 % of participants were categorized as having a middle economic status.

The use of antidepressants, regardless of their specific subclasses, was significantly associated with a increased risk of DFUs compared to non-users (adjusted IR: 1.641; 95 % CI: 1.288–2.091; Table 2). A dose-dependent increase in the risk of DFUs with cumulative antidepressant dosage was observed, with adjusted IRs (95 % CIs) of 1.934 (1.249–2.993), 1.331 (0.898–1.974), 1.605 (1.002–2.572), and 1.869 (1.226–2.851) for participants with antidepressant use of 30–60, 60–180, 180–365, and more than 365 cDDDs, respectively, in comparison to antidepressant never-users (p-for-trend: 0.0003).

The risk for DFUs based on each subclass of antidepressants are presented in Table 3. In comparison to participants who never used antidepressants, the following categories exhibited a significant association with the risk of DFUs: SSRI users (adjusted IR: 1.662; 95 % CI: 1.085–2.546), TCA users (adjusted IR: 1.670; 95 % CI: 1.196–2.332. In the analyses based on the cumulative dose of each antidepressant subclass, both SSRI and TCA use was significantly associated with DFUs, in comparison to antidepressant never-users (p-for-trend: 0.0276 for SSRI and 0.0039 for TCA).

Analyses focusing on the presence of low extremity amputation, are shown in Table 4. Antidepressant ever-users exhibited significantly higher risk in comparison to never-users (adjusted IR: 1.478; 95 % CI: 1.130–1.928 for DFUs without amputation, adjusted IR: 3.354; 95 % CI: 1.522–7.393 for DFUs with amputation). Concerning the cumulative dose of all antidepressants and TCA, both were associated with elevated IRs in cases of DFUs without amputation (p-for-trend: 0.0094 for antidepressant cumulative dose and 0.0296 for TCA cumulative dose) as well as in cases of DFUs with amputation (p-for-trend: 0.0111 for antidepressant cumulative dose and 0.0006 for TCA cumulative dose). However, there was no statistically significance in the analysis based on SSRI cumulative dose.

The relationship between individual antidepressant use, specifically TCAs and SSRIs, and the risk of DFUs is presented in Table 5. After

Table 3
Relationship between subclasses of antidepressant or cumulative dose and risk of diabetic foot ulcers.

Variables	Case (n = 791)		Control (n = 3900)		Diabetic foot ulcers									
	n	(%)	n	(%)	Crude IR	95% CI			p-for-trend	Adjusted IR[a]	95% CI			p-for-trend
Antidepressant use														
Never use (antidepressant)[b]	618	(78.13)	3424	(87.79)	1.000					1.000				
Ever use (antidepressants)	173	(21.87)	476	(12.20)										
SSRI[c,d] (never use)	114	(14.41)	309	(7.92)	**2.212**	**1.733**	-	**2.824**	**<0.0001**	1.129	0.651	-	1.959	**0.0276**
SSRI (ever use)	59	(7.46)	167	(4.28)	**2.094**	**1.524**	-	**2.877**		**1.662**	**1.085**	-	**2.546**	
30-60 cDDDs	15	(25.42)	40	(23.95)	**2.221**	**1.210**	-	**4.078**		1.683	0.834	-	3.397	
60-180 cDDDs	12	(20.34)	47	(28.14)	1.511	0.794	-	2.874		1.434	0.700	-	2.936	
180-365 cDDDs	12	(20.34)	28	(16.77)	**2.572**	**1.272**	-	**5.201**		**2.403**	**1.079**	-	**5.355**	
> 365 cDDDs	20	(33.90)	52	(31.14)	**2.282**	**1.333**	-	**3.908**		1.390	0.660	-	2.926	
SNRI[c,e] (never use)	154	(19.47)	432	(11.08)	**2.129**	**1.712**	-	**2.642**	**<0.0001**	1.131	0.648	-	1.973	0.5881
SNRI (ever use)	19	(2.40)	44	(1.13)	**2.596**	**1.468**	-	**4.592**		1.281	0.585	-	2.806	
30-60 cDDDs	5	(26.32)	11	(25.00)	2.537	0.856	-	7.522		1.961	0.589	-	6.522	
60-180 cDDDs	4	(21.05)	17	(38.64)	1.433	0.471	-	4.353		0.578	0.146	-	2.295	
180-365 cDDDs	6	(31.58)	10	(22.73)	**3.657**	**1.243**	-	**10.757**		1.603	0.391	-	6.567	
> 365 cDDDs	4	(21.05)	6	(13.64)	**4.627**	**1.208**	-	**17.721**		1.309	0.294	-	5.827	
TCA[c,f] (never use)	69	(8.72)	255	(6.54)	**1.564**	**1.170**	-	**2.089**	**<0.0001**	1.155	0.670	-	1.989	**0.0039**
TCA (ever use)	104	(13.15)	221	(5.67)	**2.963**	**2.268**	-	**3.873**		**1.670**	**1.196**	-	**2.332**	
30-60 cDDDs	24	(23.08)	59	(26.70)	**2.486**	**1.496**	-	**4.130**		1.474	0.820	-	2.653	
60-180 cDDDs	36	(34.62)	74	(33.48)	**3.061**	**1.994**	-	**4.698**		**1.909**	**1.153**	-	**3.159**	
180-365 cDDDs	22	(21.15)	46	(20.81)	**2.970**	**1.731**	-	**5.095**		1.535	0.821	-	2.870	
> 365 cDDDs	22	(21.15)	42	(19.00)	**3.534**	**2.004**	-	**6.231**		1.745	0.885	-	3.439	
Mirtazapine[c] (never use)	164	(20.73)	447	(11.46)	**2.149**	**1.744**	-	**2.649**	**<0.0001**	1.085	0.625	-	1.882	0.3975
Mirtazapine (ever use)	9	(1.14)	13	(0.33)	**2.667**	**1.212**	-	**5.870**		1.540	0.526	-	4.507	
30-60 cDDDs	2	(22.22)	1	(7.69)	2.368	0.458	-	12.250		1.068	0.159	-	7.167	
60-180 cDDDs	2	(22.22)	5	(38.46)	1.986	0.409	-	9.648		1.294	0.217	-	7.718	
180-365 cDDDs	2	(22.22)	4	(30.77)	3.619	0.589	-	22.216		1.793	0.203	-	15.800	
> 365 cDDDs	3	(33.33)	3	(23.08)	3.146	0.782	-	12.655		1.110	0.174	-	7.094	
Trazodone[c] (never use)	158	(19.97)	432	(11.08)	**2.195**	**1.771**	-	**2.720**	**<0.0001**	1.168	0.679	-	2.009	0.8864
Trazodone (ever use)	15	(1.90)	44	(1.13)	**1.964**	**1.081**	-	**3.569**		0.982	0.408	-	2.361	
30-60 cDDDs	5	(33.33)	17	(38.64)	1.643	0.598	-	4.512		1.249	0.383	-	4.078	
60-180 cDDDs	8	(53.33)	19	(43.18)	**2.477**	**1.068**	-	**5.746**		0.896	0.279	-	2.877	
> 180 cDDDs	2	(13.33)	8	(18.18)	1.468	0.310	-	6.937		0.914	0.141	-	5.905	
Tianeptine[c] (never use)	144	(18.20)	372	(9.54)	**2.319**	**1.857**	-	**2.896**	**<0.0001**	1.142	0.663	-	1.968	0.5451
Tianeptine (ever use)	29	(3.67)	104	(2.67)	**1.618**	**1.041**	-	**2.514**		1.143	0.668	-	1.953	
30-60 cDDDs	10	(34.48)	39	(37.50)	1.383	0.657	-	2.914		0.895	0.382	-	2.095	
60-180 cDDDs	13	(44.83)	38	(36.54)	**1.999**	**1.044**	-	**3.828**		1.483	0.698	-	3.152	
180-365 cDDDs	3	(10.34)	12	(11.54)	1.438	0.395	-	5.232		0.841	0.182	-	3.875	
> 365 cDDDs	3	(10.34)	15	(14.42)	1.353	0.385	-	4.753		1.309	0.327	-	5.241	
Bupropion[c] (never use)	165	(20.86)	450	(11.54)	**2.131**	**1.729**	-	**2.626**	**<0.0001**	1.036	0.598	-	1.796	0.0686
Bupropion (ever use)	8	(1.01)	14	(0.36)	**3.552**	**1.455**	-	**8.673**		2.545	0.820	-	7.898	
30-60 cDDDs	3	(37.50)	6	(42.86)	3.109	0.772	-	12.525		1.231	0.237	-	6.390	
60-180 cDDDs	3	(37.50)	6	(42.86)	3.124	0.725	-	13.457		2.251	0.328	-	15.453	
> 180 cDDDs	2	(25.00)	2	(14.29)	5.986	0.833	-	42.996		2.823	0.279	-	28.576	

Abbreviation: **Bold**, statistically significant; IR, incidence rate ratio; CI, confidence interval; cDDD, cumulative defined daily dose; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

a Adjusted for whether each antidepressant subclass was used or not, area of residence, economic status, past diagnosis prior to the index date (hypertension, myocardial infarction, heart failure, cerebrovascular disease, chronic renal disease, chronic liver disease, cancer, any psychiatric diseases), T2DM-related complications (diabetic neuropathy, diabetic angiopathy, diabetic retinopathy, diabetic nephropathy, and hemodialysis), type of antihyperglycemic medication (biguanides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and insulin), type of antihypertensive medication (calcium channel blockers, beta blockers, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, thiazides, and alpha blockers), statins, antiplatelet agents (including aspirin, clopidogrel, ticlopidine, and cilostazol), first generation antipsychotics, and second generation antipsychotics.

b All subclasses of antidepressant were prescribed lower than the threshold of the least significant prescription level (30 cDDDs).

c Prescribed lower than the threshold of the least significant prescription level (30 cDDDs).

d Including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vortioxetine.

e Including desvenlafaxine, duloxetine, milnacipran, and venlafaxine.
f Including amitriptyline, clomipramine, doxepin, and imipramine.

adjustment, it was observed that only the usage of amitriptyline was associated with a higher risk of DFUs (adjusted IR: 1.619; 95 % CI: 1.148–2.283).

In the subgroup analyses based on sex and age, particularly among males and individuals aged 60–69, significantly higher IRs for DFUs were observed (Supplementary Table 3A, B). In the sensitivity analyses encompassing alternative index dates, alternative exclusion criteria for the minimum follow-up duration, and varying cDDD thresholds for the least significant prescription level, the findings remained consistent with those of the main analyses, except for the effect of cumulative SSRI dose on the risk of DFUs (Supplementary Table 4).

4. Discussion

We investigated to ascertain the association between the utilization of antidepressants and the risk of DFUs in patients with T2DM who had not previously used antidepressants. Our study specifically centered on examining the correlation based on cumulative dose and specific subclasses of antidepressants. Additionally, we evaluated the risk of amputation in cases of DFUs and performed subgroup analyses based on age groups and sex.

Our findings indicate that individuals with T2DM who were antidepressant ever-users, particularly TCAs and SSRIs, are more likely to face an elevated risk of DFUs compared to T2DM patients who have never used antidepressants. Various potential explanations could account for this observed association. Antidepressants may have been prescribed more frequently to T2DM patients who are at a higher risk of developing DFUs. This is because depression, which is common in T2DM patients, has been linked to an increased risk of DFUs [40,41], and depression can also contribute to unhealthy lifestyles that elevate the risk of cardiovascular diseases [42]. In addition, it is possible that T2DM patients with unhealthy lifestyles, such as obesity or current smoking, are more likely to be prescribed antidepressants. Consequently, patients with a higher risk of DFUs might be more frequently prescribed these subclasses of antidepressants. However, our study accounted for several confounding factors, including complications related to T2DM and the usage of each subclass of antidepressants. The results consistently showed a higher risk of DFUs associated with specific antidepressant categories (TCAs and SSRIs), which persisted across different cumulative dose levels. Furthermore, the use of SNRIs, which are established treatment options for a major risk factor for DFUs, diabetic neuropathy, did not show an elevated risk of DFUs. These findings suggest a heightened likelihood that TCAs and SSRIs may potentially contribute to an increased risk of DFUs in patients with T2DM.

Prior research has yielded results that are consistent with the findings presented in our study. Poor glycemic control and weight gain in individuals with T2DM is recognized as a significant risk factor for the development of DFUs [43–46]. Prior research indicates that certain TCAs, such as amitriptyline, or paroxetine, an SSRI, may have antihistaminergic effects that lead to weight gain [47,48]. Antidepressant usage, particularly SSRI and TCA usage, has been associated with the risk of developing T2DM and metabolic syndrome, and the duration and dosage of antidepressant use appeared to play a substantial role in these associations [49–51]. Furthermore, the utilization of multiple subclasses of antidepressants has been correlated with higher HbA1C levels among T2DM patients, indicative of poorer glucose control [52]. However, it's important to mention that despite these associations, certain studies have not found a direct connection between antidepressant usage and the incidence of undiagnosed T2DM or insulin resistance, as demonstrated by an 18-year follow-up prospective study and a *meta*-analysis [53,54]. Additional research is necessary to uncover causality and mechanisms underlying the association between antidepressant usage and the risk of DFUs. Also, major risk factors that were not adjusted in our analyses, including BMI or smoking status, need to be considered.

In the context of selecting the initial specific antidepressant for antidepressant-naïve patients with T2DM, the use of TCAs, especially amitriptyline, and SSRIs, with a specific mention of paroxetine, which showed marginal statistical significance, should be considered as potentially harmful choices. These considerations are similar to previous research. Fluoxetine and sertraline (both SSRIs) and duloxetine (an SNRI) may be more favorable options, taking into account their potential impact on blood sugar control [55]. However, it's essential to consider mirtazapine, known for its adverse effects on appetite and weight gain [56]. In the case of bupropion, previous research has demonstrated its potential for weight loss and reducing HbA1C levels [57], making it a viable treatment option, especially for managing sexual dysfunction, a common complication of T2DM [58].

This study possesses several notable strengths, including being the first to investigate the risk of DFUs based on antidepressant use with a specific emphasis on the cumulative dose of antidepressants and their subclasses, a representative population-based design, an extensive follow-up period, and the use of prescription-based data as opposed to self-reported information. Furthermore, our focus was on assessing the impact of antidepressants on the risk of DFUs, as opposed to previous research which primarily examined sugar control, insulin resistance, or weight gain. This approach aims to offer valuable clinical insights for primary care physicians in their DFU monitoring efforts. However, there are several limitations to consider. Firstly, due to the unavailability of cohort data, we were unable to analyze several pertinent health-related factors, such as weight, smoking and alcohol consumption statuses, blood test results, and specific diagnoses encompassing psychiatric disorders, infectious diseases, and neurodegenerative conditions. Additionally, the inability to verify whether prescribed antidepressants were actually consumed by participants poses a limitation. Also, we were unable to factor in the specific reasons for antidepressant prescriptions and interactions among antidepressants in our analysis. Furthermore, potential bias may have been introduced by the earlier detection of DFUs resulting from antidepressant prescriptions. Finally, the analysis exclusively involved registered Koreans, therefore, further research is indispensable to extrapolate these findings to other racial and ethnic groups.

In conclusion, this study reveals that antidepressant usage, particularly TCAs, is linked to an increased risk of DFUs and subsequent amputation in individuals with antidepressant-naïve T2DM. Therefore, caution is advised when considering the use of antidepressants in T2DM patients, with specific attention to avoiding TCAs.

5. Ethics approval and consent to participate

All procedures were performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki. The study was approved by the Institutional Review Board of Yonsei University's Health System (4-2023-0942), which waived the need for informed consent. The requirement for informed consent was waived as the database we used in this study was based on routinely collected administrative and claims data.

Authors contributions

SYJ: conceived, designed, directed the study, critically revied the manuscript, and had primary responsibility for final content. JK: conceptualized the study, conducted statistical analysis, interpreted the data, wrote the initial draft of the manuscript, and revised the manuscript. KH and SH conducted statistical analysis, interpreted the data, and critically reviewed the manuscript. HK and ECP conducted the statistical analyses of the data and critically reviewed. SIJ: responsible for the revision of the manuscript. All authors: participated sufficiently

Table 4
Relationship between antidepressant use or cumulative dose and risk of diabetic foot ulcers without and with amputation.

Variables	Case (n = 671)		Control (n = 3308)		DFU without amputation					Case (n = 120)		Control (n = 592)		Complications with amputation				
	n	(%)	n	(%)	Adjusted IR[a]	95% CI			p-for-trend	n	(%)	n	(%)	Adjusted IR[a]	95% CI			p-for-trend
Antidepressant intake																		
Never use[b]	533	(79.43)	2909	(87.94)	1.000					85	(70.83)	515	(86.99)	1.000				
Ever use	138	(20.57)	399	(12.06)	**1.476**	**1.130**	**-**	**1.928**		35	(29.17)	77	(13.01)	**3.354**	**1.522**	**-**	**7.393**	
Cumulative dose (antidepressant)									**0.0094**									**0.0111**
30-60 cDDDs	36	(26.09)	94	(23.56)	**1.775**	**1.121**	**-**	**2.813**		6	(17.14)	16	(20.78)	2.674	0.638	-	11.213	
60-180 cDDDs	33	(23.91)	130	(32.58)	1.146	0.738	-	1.778		11	(31.43)	25	(32.47)	**4.219**	**1.269**	**-**	**14.024**	
180-365 cDDDs	28	(20.29)	75	(18.80)	1.446	0.870	-	2.403		6	(17.14)	11	(14.29)	**5.435**	**1.062**	**-**	**27.825**	
> 365 cDDDs	41	(29.71)	100	(25.06)	**1.734**	**1.087**	**-**	**2.767**		12	(34.29)	25	(32.47)	2.182	0.554	-	8.599	
Cumulative dose (TCA)[c]									**0.0296**									**0.0006**
Never use	55	(39.86)	216	(54.14)	1.079	0.602	-	1.935		14	(40.00)	39	(50.65)	1.451	0.185	-	11.373	
Ever use	83	(60.14)	183	(45.86)	**1.520**	**1.060**	**-**	**2.179**		21	(60.00)	38	(49.35)	**7.211**	**2.110**	**-**	**24.650**	
30-60 cDDDs	22	(26.51)	53	(28.96)	1.476	0.795	-	2.735		2	(5.71)	6	(7.79)	3.411	0.319	-	36.448	
60-180 cDDDs	27	(32.53)	59	(32.24)	1.670	0.956	-	2.917		9	(25.71)	15	(19.48)	**5.824**	**1.117**	**-**	**30.366**	
180-365 cDDDs	20	(24.10)	41	(22.40)	1.395	0.723	-	2.689		2	(5.71)	5	(6.49)	7.533	0.439	-	129.342	
> 365 cDDDs	14	(70.00)	30	(73.17)	1.532	0.707	-	3.319		8	(22.86)	12	(15.58)	**24.679**	**2.674**	**-**	**227.758**	
Cumulative dose (SSRI)[d]									0.2742									0.0576
Never use	93	(67.39)	253	(63.41)	1.057	0.858	-	1.910		21	(60.00)	56	(72.73)	1.061	0.131	-	8.608	
Ever use	45	(32.61)	146	(36.59)	1.383	0.863	-	2.216		14	(40.00)	21	(27.27)	3.890	0.827	-	18.296	
30-60 cDDDs	13	(28.89)	35	(23.97)	1.647	0.779	-	3.482		2	(5.71)	5	(6.49)	0.985	0.071	-	13.740	
60-180 cDDDs	10	(22.22)	42	(28.77)	1.205	0.555	-	2.616		2	(5.71)	5	(6.49)	8.636	0.600	-	124.338	
180-365 cDDDs	8	(17.78)	25	(17.12)	1.608	0.638	-	4.050		4	(11.43)	3	(3.90)	21.768	0.926	-	511.890	
> 365 cDDDs	14	(31.11)	44	(30.14)	1.137	0.487	-	2.651		6	(17.14)	8	(10.39)	2.265	0.147	-	34.813	

Abbreviation: **Bold**, statistically significant; DFU, diabetic foot ulcer; IR, incidence rate ratio cDDD, cumulative defined daily dose; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.
a Adjusted for whether each antidepressant subclass was used or not, area of residence, economic status, past diagnosis prior to the index date (hypertension, myocardial infarction, heart failure, cerebrovascular disease, chronic renal disease, chronic liver disease, cancer, any psychiatric diseases), T2DM-related complications (diabetic neuropathy, diabetic angiopathy, diabetic retinopathy, diabetic nephropathy, and hemodialysis), type of antihyperglycemic medication (biguanides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and insulin), type of antihypertensive medication (calcium channel blockers, beta blockers, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, thiazides, and alpha blockers), statins, antiplatelet agents (including aspirin, clopidogrel, ticlopidine, and cilostazol), first generation antipsychotics, and second generation antipsychotics.
b All subclasses of antidepressant were prescribed lower than the threshold of the least significant prescription level (30 cDDDs).
c Including amitriptyline, clomipramine, doxepin, and imipramine.
d Including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vortioxetine.

Table 5
Relationship between individual antidepressant use and risk of diabetic foot ulcers.

Variables	Case (n = 791)		Control (n = 3900)		Diabetic foot ulcers							
	n	(%)	n	(%)	Crude IR	95% CI			Adjusted IR[a]	95% CI		
Antidepressant use												
Never use (antidepressant)[b]	618	(78.13)	3424	(87.79)	1.000				1.000			
Ever use (antidepressants)	173	(21.87)	476	(12.20)								
TCA (never use)	69	(39.88)	255	(53.57)								
TCA (ever use)[c]	104	(60.12)	221	(46.43)								
Amitriptyline (never use)[c]	10	(5.78)	21	(4.41)	**3.278**	**1.437**	-	**7.477**	2.344	0.900	-	6.104
Amitriptyline (ever use)	94	(54.34)	200	(42.02)	**2.935**	**2.223**	-	**3.875**	**1.619**	**1.148**	-	**2.283**
Clomipramine (never use)[c]	104	(60.12)	221	(46.43)	**2.963**	**2.266**		**3.873**	**1.670**	**1.196**		**2.332**
Clomipramine (ever use)	0	(0.00)	0	(0.00)	n.a				n.a			
Doxepin (never use)[c]	103	(59.54)	220	(46.22)	**2.948**	**2.253**		**3.857**	**1.673**	**1.197**		**2.338**
Doxepin (ever use)	1	(0.58)	1	(0.21)	6.215	0.387	-	99.896	1.044	0.044	-	25.020
Imipramine (never use)[c]	96	(55.49)	203	(42.65)	**2.962**	**2.247**	-	**3.905**	**1.621**	**1.150**	-	**2.284**
Imipramine (ever use)	8	(4.62)	18	(3.78)	2.970	1.197	-	7.367	2.367	0.846	-	6.619
SSRI (never use)[c]	114	(46.72)	309	(24.90)								
SSRI (ever use)	59	(24.18)	167	(13.46)								
Citalopram (never use)[c]	58	(98.31)	162	(97.01)	**2.117**	**1.537**	-	**2.915**	**1.699**	**1.104**	-	**2.613**
Citalopram (ever use)	1	(1.69)	5	(2.99)	1.260	0.146	-	10.867	0.951	0.107	-	8.413
Escitalopram (never use)[c]	27	(45.76)	65	(38.92)	**2.507**	**1.567**	-	**4.011**	**1.921**	**1.097**	-	**3.364**
Escitalopram (ever use)	32	(54.24)	102	(61.08)	**1.840**	**1.216**	-	**2.785**	1.475	0.864	-	2.517
Fluoxetine (never use)[c]	47	(79.66)	139	(83.23)	**2.001**	**1.413**	-	**2.835**	1.560	0.981	-	2.482
Fluoxetine (ever use)	12	(20.34)	28	(16.77)	**2.589**	**1.279**	-	**5.239**	2.227	0.989	-	5.011
Fluvoxamine (never use)[c]	59	(100.00)	163	(97.60)	**2.144**	**1.559**	-	**2.949**	**1.734**	**1.132**	-	**2.655**
Fluvoxamine (ever use)	0	(0.00)	4	(2.40)	n.a				n.a			
Paroxetine (never use)[c]	47	(79.66)	141	(84.43)	**1.957**	**1.380**	-	**2.776**	**1.582**	**1.012**	-	**2.475**
Paroxetine (ever use)	12	(20.34)	26	(15.57)	**2.874**	**1.419**	-	**5.821**	2.301	0.999	-	5.301
Sertraline (never use)[c]	48	(81.36)	141	(84.43)	**2.016**	**1.425**	-	**2.852**	**1.665**	**1.072**	-	**2.587**
Sertraline (ever use)	11	(18.64)	26	(15.57)	**2.519**	**1.225**	-	**5.178**	1.677	0.671	-	4.193
Vortioxetine (never use)[c]	59	(100.00)	166	(99.40)	**2.110**	**1.535**	-	**2.901**	**1.680**	**1.096**	-	**2.577**
Vortioxetine (ever use)	0	(0.00)	1	(0.60)	n.a				n.a			

Abbreviation: **Bold**, statistically significant; DFU, diabetic foot ulcer; IR, incidence rate ratio cDDD, cumulative defined daily dose; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; n.a, not applicable.
a Adjusted for whether each antidepressant subclass was used or not, area of residence, economic status, past diagnosis prior to the index date (hypertension, myocardial infarction, heart failure, cerebrovascular disease, chronic renal disease, chronic liver disease, cancer, any psychiatric diseases), T2DM-related complications (diabetic neuropathy, diabetic angiopathy, diabetic retinopathy, diabetic nephropathy, and hemodialysis), type of antihyperglycemic medication (biguanides, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and insulin), type of antihypertensive medication (calcium channel blockers, beta blockers, angiotensin converting-enzyme inhibitors, angiotensin receptor blockers, thiazides, and alpha blockers), statins, antiplatelet agents (including aspirin, clopidogrel, ticlopidine, and cilostazol), first generation antipsychotics, and second generation antipsychotics.
b All subclasses of antidepressant were prescribed lower than the threshold of the least significant prescription level (30 cDDDs).
c Prescribed lower than the threshold of the least significant prescription level (30 cDDDs).

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CRediT authorship contribution statement

Jinhyun Kim: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Kyungduk Hurh:** Formal analysis, Methodology, Writing – review & editing. **Seokmoon Han:** Formal analysis, Methodology, Writing – review & editing. **Hyunkyu Kim:** Formal analysis, Writing – review & editing. **Eun-Cheol Park:** Formal analysis, Writing – review & editing. **Suk-Yong Jang:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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References

[1] Knol MJ, Twisk JW, Beekman AT, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837–45.
[2] Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE, et al. Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med 2010;170:1884–91.
[3] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–78.
[4] Rotella F, Mannucci E. Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. Diabetes Res Clin Pract 2013;99:98–104.
[5] De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–30.
[6] Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–42.

[7] Lustman PJ, Clouse RE. Depression in diabetic patients: the relationship between mood and glycemic control. J Diabetes Compl 2005;19:113–22.
[8] Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: a systematic review. Acta Neuropsychiatr 2017;29:127–39.
[9] Jeffery A, Maconick L, Francis E, Walters K, Wong IC, Osborn D, et al. Prevalence and characteristics of antidepressant prescribing in adults with comorbid depression and type 2 diabetes mellitus: a systematic review and meta-analysis. Health Sci Rev 2021;1:100002.
[10] Knol M, Geerlings M, Grobbee D, Egberts A, Heerdink E. Antidepressant use before and after initiation of diabetes mellitus treatment. Diabetologia 2009;52:425–32.
[11] Li C, Ford ES, Zhao G, Balluz LS, Berry JT, Mokdad AH. Undertreatment of mental health problems in adults with diagnosed diabetes and serious psychological distress: the behavioral risk factor surveillance system, 2007. Diabetes Care 2010;33:1061–4.
[12] de Ornelas Maia ACC, de Azevedo BA, Brouwers A, Nardi AE, e Silva ACdO. Prevalence of psychiatric disorders in patients with diabetes types 1 and 2. Compr Psychiatry 2012;53:1169–73.
[13] Lai Y-J, Lin C-L, Lin M-C, Lee S-T, Sung F-C, Chang Y-J, et al. Population-based cohort study on the increase in the risk for type 2 diabetes mellitus development from nonapnea sleep disorders. Sleep Med 2013;14:913–8.
[14] Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol 2012;11:521–34.
[15] Urits I, Peck J, Orhurhu MS, Wolf J, Patel R, Orhurhu V, et al. Off-label antidepressant use for treatment and management of chronic pain: evolving understanding and comprehensive review. Curr Pain Headache Rep 2019;23:1–10.
[16] Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017;376:2367–75.
[17] Frykberg RG. Diabetic foot ulcers: pathogenesis and management. Am Fam Phys 2002;66:1655–63.
[18] Reiber GE, Vileikyte L, Boyko Ed, Del Aguila M, Smith DG, Lavery LA, et al. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Diabetes Care 1999;22:157-62.
[19] International Diabetes Federation (IDF). IDF Diabetes Atlas, 10th edition. Brussels, Belgium; 2021. https://www.diabetesatlas.org.
[20] Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. Diabetes Care 2020;43:964–74.
[21] Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217–28.
[22] Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res 2020;13:1–4.
[23] Ndosi M, Wright-Hughes A, Brown S, Backhouse M, Lipsky BA, Bhogal M, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabet Med 2018;35:78–88.
[24] Petersen BJ, Linde-Zwirble WT, Tan T-W, Rothenberg GM, Salgado SJ, Bloom JD, et al. Higher rates of all-cause mortality and resource utilization during episodes-of-care for diabetic foot ulceration. Diabetes Res Clin Pract 2022;184:109182.
[25] Wu C-S, Hsu L-Y, Pan Y-J, Wang S-H. Associations between antidepressant use and advanced diabetes outcomes in patients with depression and diabetes mellitus. J Clin Endocrinol Metab 2021;106:e5136–46.
[26] Iraj B, Khorvash F, Ebneshahidi A, Askari G. Prevention of diabetic foot ulcer. Int J Prev Med 2013;4:373.
[27] Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet 2003;361:1545–51.
[28] Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJ. Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care 2018;41:645–52.
[29] Lee J, Lee JS, Park S-H, Shin SA, Kim K. Cohort profile: the national health insurance service–national sample cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15-e.
[30] Mitchell AJ. Two-week delay in onset of action of antidepressants: new evidence. Br J Psychiatry 2006;188:105–6.
[31] Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry 2005;66:148–58.
[32] Ozenç S, Simsek K, Yildirim AO, Arslan E, Sari S, Ince M, et al. Association between the development of diabetic foot and serum fetuin-A levels. Pol Arch Med Wewn 2013;123:513–8.
[33] Nyamu PN, Otieno CF, Amayo EO, McLigeyo SO. Risk factors and prevalence of diabetic foot ulcers at Kenyatta National Hospital. Nairobi East Afr Med J 2003;80:36–43.
[34] Melville A, Richardson R, McIntosh A, O'Keeffe C, Mason J, Peters J, et al. Complications of diabetes: screening for retinopathy and management of foot ulcers. Qual Health Care 2000;9:137–41.
[35] Woo YS, Bahk W-M, Seo JS, Park Y-M, Kim W, Jeong J-H, et al. The Korean medication algorithm project for depressive disorder 2021: Comparisons with other treatment guidelines. Clin Psychopharmacol Neurosci 2022;20:37.
[36] Gelenberg AJ, Freeman M, Markowitz J, Rosenbaum J, Thase M, Trivedi M, et al. American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. Am J Psychiatry 2010;167:9–118.
[37] Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. BMC Med Res Methodol 2005;5:1–6.
[38] Nicholas PJ, Boca R. Statistics for epidemiology. Danvers: Chapman and Hall/CRC; 2003.
[39] Suissa S. Brief report: the quasi-cohort approach in pharmacoepidemiology: upgrading the nested case-control. Epidemiology 2015;26:242–6.
[40] Iversen MM, Tell GS, Espehaug B, Midthjell K, Graue M, Rokne B, et al. Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT). J Diabetes Compl 2015;29:20–5.
[41] Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski P, Heckbert SR, et al. Depression and incident diabetic foot ulcers: a prospective cohort study. Am J Med 2010;123(748–54):e3.
[42] Bonnet F, Irving K, Terra J-L, Nony P, Berthezène F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis 2005;178:339–44.
[43] Merza Z, Tesfaye S. The risk factors for diabetic foot ulceration. Foot 2003;13:125–9.
[44] Wang X, Yuan C-X, Xu B, Yu Z. Diabetic foot ulcers: Classification, risk factors and management. World J Diabetes 2022;13:1049.
[45] Mariam TG, Alemayehu A, Tesfaye E, Mequannt W, Temesgen K, Yetwale F, et al. Prevalence of diabetic foot ulcer and associated factors among adult diabetic patients who attend the diabetic follow-up clinic at the University of Gondar Referral Hospital, North West Ethiopia, 2016: institutional-based cross-sectional study. J Diabetes Res 2017.
[46] Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care 1999;22:1036–42.
[47] Wang S-M, Han C, Bahk W-M, Lee S-J, Patkar AA, Masand PS, et al. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. Chonnam Med J 2018;54:101–12.
[48] Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context 2015:4.
[49] Andersohn F, Schade R, Suissa S, Garbe E. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. Am J Psychiatry 2009;166:591–8.
[50] Yoon JM, Cho E-G, Lee H-K, Park SM. Antidepressant use and diabetes mellitus risk: a meta-analysis. Korean J Fam Med 2013;34:228.
[51] van Reedt Dortland AK, Giltay EJ, Van Veen T, Zitman FG, Penninx BW. Metabolic syndrome abnormalities are associated with severity of anxiety and depression and with tricyclic antidepressant use. Acta Psychiatr Scand 2010;122:30–9.
[52] Kammer JR, Hosler AS, Leckman-Westin E, DiRienzo G, Osborn CY. The association between antidepressant use and glycemic control in the Southern Community Cohort Study (SCCS). J Diabetes Compl 2016;30:242–7.
[53] Kivimäki M, Batty GD, Jokela M, Ebmeier KP, Vahtera J, Virtanen M, et al. Antidepressant medication use and risk of hyperglycemia and diabetes mellitus—a noncausal association? Biol Psychiatry 2011;70:978–84.
[54] Van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. Gen Hosp Psychiatry 2010;32:380–95.
[55] Deuschle M. Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. Curr Opin Psychiatry 2013;26:60–5.
[56] Anttila SA, Leinonen EV. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev 2001;7:249–64.
[57] Lustman PJ, Williams MM, Sayuk GS, Nix BD, Clouse RE. Factors influencing glycemic control in type 2 diabetes during acute-and maintenance-phase treatment of major depressive disorder with bupropion. Diabetes Care 2007;30:459–66.
[58] Sayuk GS, Gott BM, Nix BD, Lustman PJ. Improvement in sexual functioning in patients with type 2 diabetes and depression treated with bupropion. Diabetes Care 2011;34:332–4.