Association Between the Use of Antidepressants and the Risk of Type 2 Diabetes: A Large, Population-Based Cohort Study in Japan

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OBJECTIVE

This study aimed to reveal the associations between the risk of new-onset type 2 diabetes and the duration of antidepressant use and the antidepressant dose, and between antidepressant use after diabetes onset and clinical outcomes.

RESEARCH DESIGN AND METHODS

In this large-scale retrospective cohort study in Japan, new users of antidepressants (exposure group) and nonusers (nonexposure group), aged 20–79 years, were included between 1 April 2006 and 31 May 2015. Patients with a history of diabetes or receipt of antidiabetes treatment were excluded. Covariates were adjusted by using propensity score matching; the associations were analyzed between risk of new-onset type 2 diabetes and the duration of antidepressant use/dose of antidepressant in the exposure and nonexposure groups by using Cox proportional hazards models. Changes in glycated hemoglobin (HbA_{1c}) level were examined in groups with continuous use, discontinuation, or a reduction in the dose of antidepressants.

RESULTS

Of 90,530 subjects, 45,265 were in both the exposure and the nonexposure group after propensity score matching; 5,225 patients (5.8%) developed diabetes. Antidepressant use was associated with the risk of diabetes onset in a time- and dose-dependent manner. The adjusted hazard ratio was 1.27 (95% CI 1.16–1.39) for short-term low-dose and 3.95 (95% CI 3.31–4.72) for long-term high-dose antidepressant use. HbA_{1c} levels were lower in patients who discontinued or reduced the dose of antidepressants ($F[2,49] = 8.17$; $P < 0.001$).

CONCLUSIONS

Long-term antidepressant use increased the risk of type 2 diabetes onset in a time- and dose-dependent manner. Glucose tolerance improved when antidepressants were discontinued or the dose was reduced after diabetes onset.

Antidepressants are widely prescribed in developed countries (1). Selective serotonin reuptake inhibitors (SSRIs) are prescribed for psychiatric disorders such as depression, anxiety disorder, panic disorder, and obsessive-compulsive disorder; the prescription rate is ~1.5% in Japan (2). We know empirically that patients who have been taking

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antidepressants for a long time are prone to impaired glucose tolerance and that glucose tolerance improves after antidepressants are discontinued. An observational study (3) and a case-control study (4) previously suggested an association between long-term antidepressant use and the risk of developing type 2 diabetes. However, several observational studies did not confirm this significant association (5–8). Such discrepancies may be due to the study design and sample size, biased assessment of antidepressant exposure, confounding factors, and patient characteristics. Among confounding factors, depression is an independent risk factor of type 2 diabetes (9,10). However, the associations among depression, antidepressants, and type 2 diabetes remain unclear, as do the mechanisms. Type 2 diabetes is more strongly associated with antidepressant use than with depression (11). A case-control study in Taiwan showed that antidepressant use for ≥2 years increased the risk of type 2 diabetes (12), but such an association has not yet been investigated in Japan. It would be clinically important to evaluate the association between antidepressant and type 2 diabetes among various Asian ethnicities, using an adequate sample size after considering the confounding factors. The results of this research can fill in the knowledge gap by adding new information to the existing literature, particularly that the use of antidepressants also increases the risk of type 2 diabetes in Japanese, and the risk increases in relation to dose and duration. Furthermore, to our knowledge, no studies have investigated the status of antidepressant use in patients who developed type 2 diabetes after taking antidepressants; as a result, the association between antidepressant use and the clinical outcome of type 2 diabetes is unknown. Identifying racial differences in the relationship between antidepressant use and diabetes, as well as the clinical outcomes after adjusting for antidepressant use, can better inform the selection of a treatment option for patients. Therefore, this study aimed to determine the associations between the risk of new-onset type 2 diabetes and the duration of antidepressant use and dose of antidepressant, and between antidepressant use after type 2 diabetes onset and clinical outcomes.

RESEARCH DESIGN AND METHODS

Study Design

This was a retrospective cohort study in which we used linked anonymized data from medical claims and health checks for 3,382,567 employees and their family members, aged 20–79 years, who were insured by the five main employee health insurance associations in Japan; the data were provided by JMDC Inc. (Tokyo, Japan). The data identification technology used by JMDC links individual monthly medical claims to the corresponding health check results, enabling continuous follow-up of individuals' history of medical care without revealing personally identifiable information. The population comprised individuals who were insured between 1 April 2005 and 30 April 2016 and had information about joining or leaving the insurance programs, or both. Clinical claims data and health check data were extracted monthly. A 110-month cohort entry period was used, starting in April 2006 and ending in May 2015, and patients prescribed antidepressants were extracted. The antidepressants used by those patients are listed in Supplementary Table 1.

The date of cohort entry was defined as the month of the first prescription of an antidepressant. Inclusion criteria were *1*) age 20–79 years and *2*) information available for prescriptions and health check results during the 12-month period before and the 12-month period after cohort entry. Exclusion criteria were any of the following within the 12-month period before cohort entry: *1*) a prescription for an antidepressant, *2*) a prescription for an antidiabetes treatment, *3*) glycated hemoglobin (Hb_{A1c}) ≥6.5% (per the National Glycohemoglobin Standardization Program [NGSP]), and *4*) diagnosis of type 1 diabetes in medical claims data (ICD-10 code E10.x) (13). The observation period was from the date of cohort entry to April 2016. Data were censored when any of the following occurred: *1*) type 2 diabetes onset, *2*) leaving an employee health insurance association, *3*) death, *4*) end of the observation period, *5*) change in prescribed antidepressant medication(s), or *6*) missing prescriptions for ≥3 months (i.e., no prescription in the 4th month since the first prescription). Prescription of antidepressants was a risk factor for developing type 2 diabetes. The durations of exposure and nonexposure were defined as the number of months when an antidepressant was prescribed and not prescribed, respectively. Although no concrete evidence exists about the time required for glucose tolerance to become impaired in patients taking antidepressants, it is ∼ ≥1 year (4,11,14). Accordingly, prescription for only 1 month and prescriptions that changed were not included in the prescription period. When prescriptions were missed for 1–3 months, those months were included in the exposure period, because clear evidence regarding the duration of the effect of antidepressants on glucose tolerance is lacking, and in previous studies, the exposure period included up to 3 months after an antidepressant prescription had been discontinued (4).

Ethical Considerations

The medical claims and health check data were initially provided by main employee health insurance associations in Japan to JMDC, which linked and anonymized the data using identifiers before providing them to the National Center of Neurology and Psychiatry. Identifiers were unique to the data set provided, and no personally identifiable information was attached. Consent for using information was obtained from the patients who underwent a health checkup.

Definitions of Variables, End Points, and Confounding Factors

The primary end point was type 2 diabetes onset, defined as *1*) a first prescription of antidiabetes drugs or insulin injections in monthly medical claims data or *2*) HbA_{1c} ≥6.5% (per the National Glycohemoglobin Standardization Program) in health check data (13). Predictors of risk were depression, duration of antidepressant use, mean monthly dose of prescribed antidepressant(s), and use of combined antidepressants. Three categories were defined for the duration of antidepressant use: short term (<12 months), intermediate term (12–24 months), and long term (≥25 months). The mean monthly dose of prescribed antidepressants was calculated by dividing the cumulative antidepressant dose prescribed during the prescription duration (converted to amitriptyline equivalents) by the prescription duration (months). Three categories were defined for the mean monthly dose of prescribed antidepressants: low dose (<91.4), moderate dose (91.4–182.8), and high dose (≥182.9). The median monthly dose among all patients with an antidepressant prescription was 91.4; this value was the reference value

for categorization. Thus, nine categories were derived on the basis of the combination of the prescription duration and the mean monthly dose. Antidepressants were grouped as tricyclic antidepressants (TCAs), tetracyclic antidepressants (TTAs), SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), and others (mirtazapine, sulpiride, and trazodone).

The covariates for adjusting of confounding factors were age, sex, underlying diseases (hypertension, dyslipidemia, cardiovascular diseases, and schizophrenia), BMI at the start of observation, alcohol intake, smoking status, exercise habits, and late-evening snacking. Drugs possibly associated with risk of type 2 diabetes (β-receptor blockers, carbamazepine, steroids, lithium carbonate, phenytoin, thiazide diuretics, valproic acid, antipsychotics including multiacting receptor-targeted antipsychotics [MARTAs], and statins) (15,16) were included as covariates when used during the 3-month period before cohort entry and during the observation period. Ten-year age groups were used. The presence of hypertension was defined as ICD-10 code I10 or code I15, or a prescription for an antihypertensive drug in the data. The presence of dyslipidemia was defined as LDL cholesterol ≥140 mg/dL noted in health check data or a prescription for an antidyslipidemia drug. The presence of other conditions was defined as diagnoses in medical claims data. Alcohol intake categories were <180, 180–359, 360–539, and≥540 mL/day. BMI categories were underweight/normal (<25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). The presence of depression was defined as ICD-10 codes F32.x (depressive episodes), F33.x (recurrent depressive disorder), F34.x (persistent mood disorders), F38.x (other mood disorders), and F39 (unspecified mood disorder); other mental disorders were defined as codes F00–F09 (organic, including symptomatic, mental disorders), F30-F31 (bipolar affective disorders), F40—F48 (neurotic, stress-related, and somatoform disorders), and F50–F51 (eating and nonorganic sleep disorders).

Among patients with new-onset type 2 diabetes after antidepressant use, data were extracted for those who were not prescribed an antidiabetes drug, had 2-year follow-up data on antidepressant prescription status, and had changes in HbA_{1c} level after type 2 diabetes onset. These patients were then divided into three groups according to antidepressant prescription status: continuation, discontinuation, and dose reduction (defined as a ≥50% reduction from the dose at type 2 diabetes onset). The proportion of patients who switched medications during this follow-up period was small (≤1% of all patients), and they were excluded.

Statistical Procedures

Missing data for lifestyle items (i.e., alcohol intake, smoking status, exercise habits, and late-evening snacking) were replaced by using multiple imputations. No data were missing for other covariates. One-to-one propensity score matching was performed in order to adjust for confounding factors (17). In one-to-one matching, each patient in the exposure group was paired with a patient in the nonexposure group on the basis of propensity score. This technique avoids unbalanced sample sizes between groups, thus avoiding loss of statistical power (18). Propensity scores were calculated by logistic regression with the covariates age, sex, underlying diseases, BMI, lifestyle factors (alcohol intake, smoking status, exercise habits, and late-evening snacking), and use of concomitant medications. Nearest-neighbor matching within the caliper was used. The number of individuals who can be matched increases as the caliper becomes bigger. The recommended caliper size is 0.20–0.25 SDs (19,20); this study used a caliper of 0.2 SDs.

First, we investigated the association between depression and risk of new-onset type 2 diabetes. Four groups with different combinations of mental disorder type (depression or nondepression) and antidepressant prescription status (exposure or nonexposure) were compared with the group with antidepressant exposure and no mental disorder by using the Cox proportional hazards model. Next, we investigated the associations between the duration of antidepressant use/dose of antidepressant and the risk of type 2 diabetes onset using a Cox proportional hazards model. Nine groups with different combinations of duration of antidepressant use (short-, intermediate-, or long-term) and dose of antidepressant (low, moderate, or high) were compared with the group that did not use antidepressants. Afterward, the effect of combined antidepressants on the risk of type 2 diabetes onset was analyzed by using the Cox proportional hazards model with the group that did not use antidepressants. Last, changes in the HbA_{1c} level during follow-up after type 2 diabetes onset were compared among the three antidepressant prescription statuses (continuation, discontinuation, and dose reduction) by using the Tukey-Kramer multiple comparison test. A P value <0.05 was considered statistically significant in all analyses. SPSS version 24.0 (IBM, Armonk, NY) was used for statistical analysis.

RESULTS

Selection and Subjects

A total of 761,247 individuals met the inclusion criteria. After excluding those who had been prescribed an antidiabetes drug or had HbA_{1c} ≥6.5% before study entry (n = 1,830), 50,770 were allocated to the exposure group and 708,647 to the nonexposure group. The flowchart showing patient inclusion and exclusion is shown in Supplementary Fig. 1. After adjustment, 69% of subjects were male, 33% were smokers, and 78% were hypertensive. A C statistic of 0.71 was used in propensity score models. Characteristics of the exposure and nonexposure groups before and after matching are shown in Table 1. After matching, the exposure group comprised 45,265 patients (31,192 men and 14,073 women; mean ± SD age 41.4 ± 9.6 years), and the nonexposure group comprised 45,265 patients (31,219 men and 14,046 women; mean ± SD age 46.8 ± 10.4 years). SSRIs were prescribed to 25.8% of patients who used an antidepressant, SNRIs to 6.0%, TCAs to 5.4%, two antidepressants to 20.2%, and three or more antidepressants to 14.9%. The percentage of subjects using two or more antidepressants is shown in Supplementary Table 2.

Risk of New-Onset Type 2 Diabetes Associated With Antidepressants

Type 2 diabetes onset occurred in 5,225 individuals (5.8%): 1,950 (170,246.7 person-years) in the exposure group and 3,275 (407,875.1 person-years) in the nonexposure group. The adjusted hazard ratio (HR) for each group is listed in Table 2. There was no association for those with depression who were not using antidepressants (HR 1.10; 95% CI 0.85–1.43; P = 0.47). However, the "Depression, not using antidepressants" group had a small sample size (~1% of the total). In contrast, a significant association was confirmed in all nine groups with different combinations of duration of

Table 1—Subject characteristics

	Before adjustment by matching		After adjustment by matching	
	Exposure group (n = 50,770)	Nonexposure group (n = 708,647)	Exposure group (n = 45,265)	Nonexposure group (n = 45,265)
Observation time, person-years, *n*	193,925.75	6,463,947.08	170,246.67	407,875.08
Patients with onset of diabetes, *n*	2,394	39,775	1,950	3,275
Patients with onset of diabetes per 1,000 person-years, *n*	12.34	7.48	11.45	8.03
Age at the start of observation, mean (SD), years	41.5 (9.6)	43.7 (10.1)	41.4 (9.6)	46.8 (10.4)
Observation time, mean (SD), years	3.8 (2.8)	9.1 (2.6)	3.8 (2.7)	9.0 (2.9)
Male sex	34,987 (68.9)	475,168 (67.1)	31,192 (68.9)	31,219 (69.0)
Age (years)				
20–29	3,033 (6.0)	63,021 (8.9)	2,770 (6.1)	2,800 (6.2)
30–39	8,569 (16.9)	180,384 (25.5)	7,735 (17.1)	7,690 (17.0)
40–49	17,395 (34.3)	261,232 (36.9)	15,532 (34.3)	15,261 (33.7)
50–59	15,733 (31.0)	154,492 (21.8)	13,828 (30.5)	14,044 (31.0)
60–69	5,392 (10.6)	47,043 (6.6)	4,821 (10.7)	4,871 (10.8)
70–79	648 (1.3)	2,475 (0.3)	579 (1.3)	597 (1.3)
BMI category				
Normal/underweight	33,928 (66.8)	495,429 (69.9)	30,840 (68.1)	31,032 (68.6)
Overweight	13,490 (26.6)	175,479 (24.8)	11,660 (25.8)	11,545 (25.5)
Obese	3,352 (6.6)	37,739 (5.3)	2,765 (6.1)	2,688 (5.9)
Smoking status				
Current smoker	16,884 (33.3)	225,338 (31.8)	14,858 (32.8)	14,977 (33.1)
Ex-smoker/never-smoker	33,886 (66.7)	483,309 (68.2)	30,407 (67.2)	30,288 (66.9)
Physical activity (days/week)				
3	27,309 (53.8)	382,029 (53.9)	24,467 (54.1)	24,552 (54.2)
2 or 0	23,461 (46.2)	326,618 (46.1)	20,798 (45.9)	20,713 (45.8)
Alcohol intake (mL/day)				
<180	30,917 (60.9)	401,704 (56.7)	27,244 (60.2)	27,158 (60.0)
180–359	11,044 (21.8)	172,731 (24.4)	10,032 (22.2)	10,107 (22.3)
360–539	6,066 (11.9)	95,061 (13.4)	5,507 (12.2)	5,555 (12.3)
≥540	2,743 (5.4)	39,151 (5.5)	2,482 (5.5)	2,445 (5.4)
Late-evening snacking				
No	22,880 (45.1)	353,212 (49.8)	20,481 (45.2)	20,579 (45.5)
Yes	27,890 (54.9)	355,435 (50.2)	24,784 (54.8)	24,686 (54.5)
Underlying conditions				
Hypertension				
Yes	40,088 (79.0)	553,394 (78.1)	35,703 (78.9)	35,527 (78.5)
No	10,682 (21.0)	155,253 (21.9)	9,562 (21.1)	9,738 (21.5)
Dyslipidemia/statin prescription				
No dyslipidemia	27,715 (54.6)	418,591 (59.1)	35,703 (78.9)	35,527 (78.5)
Dyslipidemia/no statin	493 (1.0)	2,944 (0.4)	383 (0.8)	371 (0.8)
Dyslipidemia/statin	22,562 (44.4)	287,112 (40.5)	19,810 (43.8)	19,751 (43.6)
Cardiovascular diseases	4,060 (8.0)	33,758 (4.8)	3,482 (7.7)	3,608 (8.0)
Schizophrenia	123 (0.2)	1,186 (0.2)	121 (0.3)	145 (0.3)
Concomitant medications				
Antipsychotic				
MARTA	4,269 (8.4)	1,270 (0.2)	1,197 (2.6)	966 (2.1)
Non-MARTA	9,714 (19.1)	5,559 (0.8)	4,425 (9.8)	4,595 (10.2)
β-Blocker	3,899 (7.7)	25,115 (3.5)	3,158 (7.0)	3,275 (7.2)
Carbamazepine	490 (1.0)	1,053 (0.1)	294 (0.6)	321 (0.7)
Steroid	2,339 (4.6)	30,812 (4.3)	2,064 (4.6)	2,035 (4.5)
Lithium carbonate	1,857 (3.7)	410 (0.1)	647 (1.4)	395 (0.9)
Phenytoin	59 (0.1)	432 (0.1)	50 (0.1)	62 (0.1)
Thiazide diuretic	674 (1.3)	6,558 (0.9)	577 (0.3)	585 (1.3)
Valproic acid	2,843 (5.6)	2,046 (0.3)	1,366 (3.0)	1,412 (3.1)

Data are *n* (%) unless otherwise indicated. MARTA, multiacting receptor-targeted antipsychotic.

antidepressant use and dose of antidepressant, from the short-duration low-dose group (HR 1.27; 95% CI 1.16–1.39; $P <$ 0.001) to the long-duration high-dose group (HR 3.95; 95% CI 3.31–4.72; $P <$ 0.001).

Analysis results for combined antidepressants are shown in Supplementary Table 2. A significant association was

confirmed for use of any single type of antidepressant: TCA, HR 2.33 (95% CI 1.93–2.81); TTA, HR 2.99 (95% CI 2.06–4.35); SSRI, HR 1.59 (95% CI 1.43–1.76); and SNRI, HR 2.39 (95% CI 1.96–2.91). Almost all of the combinations of antidepressants showed a significant association; only the combination of TTA and trazodone did not.

Clinical Outcomes of Type 2 Diabetes That Developed After Antidepressant Use

The results of follow-up after type 2 diabetes onset are shown in Tables 3 and 4 and in Supplementary Fig. 2. Among 1,950 patients with new-onset type 2 diabetes in the exposure group, 1,651 had a prescription for antidiabetes drugs or insulin injections, and 1 among the remaining 299 switched medications. The other 298 were followed up. SSRIs were prescribed to 33.9%, sulpiride to 20.1%, TCAs to 13.6%, and SNRIs to 13.4%. Among those who developed type 2 diabetes while they were receiving antidepressant therapy, 199 patients did not take antidiabetes drugs and continued the same antidepressant therapy.

HbA_{1c} levels were significantly lower in the discontinuation and dose reduction groups than in the continuation group. ANOVA showed that the results were significant, with an $F(2,262)$ of 4.93 ($P = 0.008$) at year 1 after onset, $F(2,131)$ of 9.25 ($P < 0.001$) at year 2 after onset, and $F(2,49)$ of 8.17 ($P < 0.001$) at year 3 after onset. The Tukey-Kramer multiple comparison test showed significant differences between the continuation and discontinuation groups and between the continuation and dose reduction groups at years 1, 2, and 3 after onset. HbA_{1c} levels returned to the normal range in 97.5% of patients (79 of 81) in the discontinuation group and in 94.0% (63 of 67) in the dose reduction group; the difference was not significant.

CONCLUSIONS

Effect of Antidepressants on the Risk of Type 2 Diabetes Onset

The use of antidepressants increased the risk of new-onset type 2 diabetes in a time- and dose-dependent manner. The relative risk of type 2 diabetes onset was high in patients prescribed high doses of antidepressants for ≥2 years. Moreover, antidepressant monotherapy was significantly associated with type 2 diabetes risk. Combination therapies of two or more antidepressants also showed a significant association with type 2 diabetes risk, although 95% CIs were large for some antidepressant combinations, owing to the small sample size. Therefore, we cannot simply conclude that combination therapy increases the risk of type 2 diabetes. Further studies with larger sample sizes are needed.

Mechanism of Antidepressant-Induced Diabetes

We confirmed that all antidepressant monotherapies and combination therapies, except the combination of a TTA and trazodone, had a significant association with type 2 diabetes risk. This suggests that TCAs, TTAs, SSRIs, SNRIs, and other antidepressants individually have a risk of causing type 2 diabetes. Mechanisms

Table 2—Use of antidepressants and risk of new-onset type 2 diabetes

	No onset of diabetes (n = 85,305)	Onset of diabetes (n = 5,225)	Person-years, n	Adjusted incidence rate[a]	Cox proportional hazards model		
					Adjusted HR[a]	95% CI	P value
Use of antidepressants and depression							
No mental disorders, using antidepressants (reference category)	35,562 (41.7)	2,763 (52.9)	352,252.75	1.00	—	—	—
Depression, using antidepressants	16,309 (19.1)	830 (15.9)	63,681.17	1.66	1.90	1.75–2.07	<0.001
Depression, not using antidepressants	671 (0.8)	58 (1.1)	6,563.50	1.13	1.10	0.85–1.43	0.47
Use of antidepressants							
None (reference category)	41,990 (49.2)	3,275 (62.7)	407,875.08	1.00	—	—	—
Short-term, low dose	23,920 (28.0)	646 (12.4)	79,297.92	1.01	1.27	1.16–1.39	<0.001
Short-term, moderate dose	2,855 (3.3)	101 (1.9)	9,275.83	1.36	1.77	1.45–2.17	<0.001
Short-term, high dose	332 (0.4)	19 (0.4)	1,189.50	1.99	2.54	1.62–3.99	<0.001
Intermediate-term, low dose	3,900 (4.6)	135 (2.6)	15,602.00	1.08	1.44	1.21–1.72	<0.001
Intermediate-term, moderate dose	1,691 (2.0)	91 (1.7)	6,204.00	1.83	2.52	2.04–3.11	<0.001
Intermediate-term, high dose	310 (0.4)	23 (0.4)	1,189.42	2.41	3.32	2.20–5.01	<0.001
Long-term, low dose	6,097 (7.1)	478 (9.1)	33,420.92	1.78	2.14	1.94–2.36	<0.001
Long-term, moderate dose	3,415 (4.0)	329 (6.3)	19,234.08	2.13	2.58	2.30–2.89	<0.001
Long-term, high dose	795 (0.9)	128 (2.4)	4,833.00	3.30	3.95	3.31–4.72	<0.001

Data are n (%) unless otherwise indicated. [a]HRs were adjusted for sex, age, BMI, smoking status, exercise, alcohol intake, late-evening snacking, underlying conditions, and concomitant medications.

Table 3—Clinical outcomes and characteristics of patients who developed diabetes after using antidepressants

		Antidepressant use		
	All patients (n = 298)	Continuation (n = 150)	Discontinuation (n = 81)	Dose reduction (n = 67)
Observation time, *n*, person-years	644.25	348.83	156.08	139.33
Age at the start of observation, mean (SD), years	50.4 (9.0)	50.4 (9.0)	51.3 (9.2)	49.2 (8.7)
Observation time, mean (SD), years	2.2 (1.9)	2.3 (2.0)	1.9 (1.8)	2.1 (1.9)
Male sex	236 (79.2)	121 (80.7)	65 (80.2)	50 (74.6)
Age, years				
20–29	6 (2.0)	1 (0.7)	1 (1.2)	4 (6.0)
30–39	24 (8.1)	14 (9.3)	6 (7.4)	4 (6.0)
40–49	108 (36.2)	58 (38.7)	27 (33.3)	23 (34.3)
50–59	114 (38.3)	55 (36.7)	32 (39.5)	27 (40.3)
60–69	42 (14.1)	19 (12.7)	14 (17.3)	9 (13.4)
70–79	4 (1.3)	3 (2.0)	1 (1.2)	0 (0.0)
BMI category				
Normal/underweight	98 (32.9)	42 (28.0)	35 (43.2)	21 (31.3)
Overweight	121 (40.6)	74 (49.3)	20 (24.7)	27 (40.3)
Obese	79 (26.5)	34 (22.7)	26 (32.1)	19 (28.4)
Smoking status				
Current smoker	116 (38.9)	60 (40.0)	33 (40.7)	23 (34.3)
Ex-smoker/never-smoker	182 (61.1)	90 (60.0)	48 (59.3)	44 (65.7)
Physical activity, days/week				
3	171 (57.4)	84 (56.0)	48 (59.3)	39 (58.2)
2 or 0	127 (42.6)	66 (44.0)	33 (40.7)	28 (41.8)
Alcohol intake, mL/day				
<180	201 (67.4)	100 (66.7)	61 (75.3)	40 (59.7)
180–359	49 (16.4)	25 (16.7)	11 (13.6)	13 (19.4)
360–539	34 (11.4)	19 (12.7)	5 (6.2)	10 (14.9)
≥540	14 (4.7)	6 (4.0)	4 (4.9)	4 (6.0)
Late-evening snacking				
No	114 (38.3)	83 (55.3)	34 (42.0)	27 (40.3)
Yes	154 (51.7)	67 (44.7)	47 (58.0)	40 (59.7)
Underlying conditions				
Hypertension				
Yes	175 (58.7)	84 (55.3)	47 (58.0)	44 (65.7)
No	123 (41.3)	66 (44.0)	34 (42.0)	23 (34.3)
Dyslipidemia/statin prescription				
No dyslipidemia	86 (28.9)	44 (29.3)	26 (32.1)	16 (23.9)
Dyslipidemia/no statin	8 (2.7)	6 (4.0)	0 (0.0)	2 (3.0)
Dyslipidemia/statin	204 (68.5)	100 (66.7)	55 (67.9)	49 (73.1)
Cardiovascular diseases	49 (16.4)	26 (17.3)	11 (13.6)	12 (17.9)
Schizophrenia	2 (0.7)	1 (0.7)	1 (1.2)	0 (0.0)
Concomitant medications				
Antipsychotics				
MARTA	33 (11.1)	19 (12.7)	6 (7.4)	8 (11.9)
Non-MARTA	83 (27.9)	45 (30.0)	20 (24.7)	18 (26.9)
Beta blockers	43 (14.4)	21 (14.0)	12 (14.8)	10 (14.9)
Carbamazepine	4 (1.3)	1 (0.7)	0 (0.0)	3 (4.5)
Steroids	17 (5.7)	11 (7.3)	6 (7.4)	0 (0.0)
Lithium carbonate	22 (7.4)	13 (8.7)	4 (4.9)	5 (7.5)
Phenytoin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thiazide diuretics	4 (1.3)	2 (1.3)	0 (0.0)	2 (3.0)
Valproic acid	35 (11.7)	16 (10.7)	6 (7.4)	13 (19.4)

Data are *n* (%) unless otherwise indicated. MARTA, multiacting receptor-targeted antipsychotic.

explaining the association between new-onset type 2 diabetes and antidepressant use are unclear. Antidepressant use increases the risk of weight gain, although the association with diabetes cannot be explained solely by weight gain (21). Various mechanisms have been reported for TCA- and SSRI-induced diabetes. Clomipramine, a TCA, selectively inhibits the 5-HT_{2c} receptor, thereby altering glucose regulation (22). In contrast, SSRIs activate glycogen synthase kinase 3β to inhibit insulin-induced tyrosine phosphorylation of insulin receptor substrate-2, thereby promoting insulin resistance, and they inhibit insulin secretion to induce the unfolded protein response and apoptosis of pancreatic β-cells (23). In experimental

Table 4—Tukey-Kramer multiple comparisons

	SE	95% CI	*P* value
Year 1 after onset			
Continuation vs. discontinuation	0.14	0.05–0.69	0.02
Continuation vs. dose reduction	0.14	0.002–0.68	0.05
Year 2 after onset			
Continuation vs. discontinuation	0.16	0.29–1.07	<0.001
Continuation vs. dose reduction	0.18	0.08–0.91	0.02
Year 3 after onset			
Continuation vs. discontinuation	0.23	0.28–1.41	0.002
Continuation vs. dose reduction	0.20	0.12–1.09	0.01

animals, maprotiline, an SNRI, did not increase blood glucose levels (24), suggesting that SNRIs have a distinct hyperglycemia-inducing mechanism. Thus different classes of antidepressants may induce hyperglycemia through distinct pathways and have different diabetes-related risks.

Comparisons With Related Studies

This study showed that diabetes risk depends on the duration of antidepressant use, which is consistent with the results of previous observational studies (4,11,25–27). Among 52,326 women, in a study led by the Woman's Health Initiative, antidepressant use was associated with increased risk of new-onset diabetes after adjustment for depressive symptoms, BMI, age, ethnicity, education, physical activity, smoking status, and family history of diabetes (HR 1.32; 95% CI 1.19–1.47) (27). In the current study, data were not available for some non-Japanese individuals insured by the employee health insurance associations. However, the majority of employees are Japanese according to the data published by the Ministry of Health, Labour and Welfare (28); thus, ethnicity was not included in the covariates in this study. A nested case-control study in the U.K. showed an increased risk of diabetes when moderate to high doses of antidepressants were used for ≥2 years, and that among several classes of antidepressants, SSRIs and TCAs were associated with high diabetes risk (4). This study, however, showed that use of other antidepressants, as well as SSRIs and TCAs, at low doses for <2 years was significantly associated with risk of diabetes. Therefore, further studies are needed to assess whether there are differences in vulnerability to antidepressant-induced diabetes among ethnicities and to identify which classes of antidepressants are associated with diabetes risk. In contrast, several observational studies did not find an association between antidepressant use and diabetes (29–31). Possible reasons include that risk of diabetes was a secondary end point, assessment of exposure may be biased when using self-reported data, and assessment of the exposure duration was inadequate.

Clinical Outcomes of Type 2 Diabetes That Developed After Antidepressant Use

In this study, patients with new-onset diabetes after antidepressant use were followed up. To our knowledge, this is the first study that followed the clinical course after type 2 diabetes onset in patients taking antidepressants. Among those who developed type 2 diabetes while they were receiving antidepressant therapy, 10.2% (199 of 1,950) did not take antidiabetes drugs and continued the same antidepressant therapy. Medical claims data do not explain why physicians continued prescribing the same antidepressants; however, physicians might not suspect the association between antidepressants and type 2 diabetes onset or might underestimate the effect of antidepressants. Among patients who developed type 2 diabetes, HbA_{1c} levels improved when antidepressant therapy was discontinued or the dose was reduced by ≥50%. HbA_{1c} levels returned to the normal range in most patients in the discontinuation group (97.5%) and the dose reduction group (94.0%), indicating that modifying the antidepressant dose was effective in improving glucose tolerance. Our results suggest that reducing the dose of or discontinuing causative antidepressants within 1 year of type 2 diabetes onset alleviates impaired glucose tolerance, which in turn strongly suggests a causal relationship between antidepressant administration and type 2 diabetes onset. However, exercise and dietary interventions might have been required in patients who developed type 2 diabetes; therefore, we cannot conclude that discontinuation or reduction of the dose of antidepressants was solely responsible for alleviating the impaired glucose tolerance. It is noteworthy that glucose tolerance remained impaired in some patients. This study had a small sample size, and therefore the results cannot be generalized. Further investigation of large samples is required.

Clinical Impact

The medical costs associated with diabetes are very high. According to the U.S. Centers for Disease Control and Prevention, 30.3 million Americans had diabetes and 84.1 million had prediabetes in 2015 (32). In Japan, the number of patients with diabetes increased from 4.7 million in 1980 to 10.8 million in 2014. Annual medical costs of diabetes have increased to 90 trillion yen worldwide, of which 4 trillion was spent in Japan in 2016 (32). Persistent impairment of blood glucose control leads to complications such as nephropathy, retinopathy, and neurological disorders—all of which are included in the medical costs of diabetes, in addition to the disease itself. To control medical costs, diabetes onset due to antidepressants should be considered when patients with a high risk of diabetes are offered treatment with antidepressants (33).

Study Limitations

This study had several limitations. First, even though confounding factors were adjusted for by propensity score matching, the results of this study might not be applicable to unmatched subjects. Moreover, residual confounding due to differences in unmeasured factors was not considered. The number of patients with diabetes in the model adjusted for covariates was about 1.7 times higher in the unexposed group than in the exposed group. This difference may have occurred because kidney function and medication status were not included as covariates. Second, the study population was employees and their family members insured by employee health insurance associations; therefore, not many children and elderly individuals were included. Third, this study regarded antidepressant prescriptions as indicating exposure to antidepressants, but

patients' actual adherence to medication regimens was unknown and not taken into account. Fourth, to perform interclass analysis of antidepressants, observation was terminated when antidepressants were changed; thus the number of patients who developed type 2 diabetes after switching medications might be underestimated. Fifth, although some subjects in this study may have had transient hypertension, such as white coat hypertension, it was difficult to determine from their data whether they had true hypertension. Sixth, if antidepressants were discontinued because depression had been cured, physical activity increased and thus HbA_{1c} levels may have improved. Further studies adjusting for the depression scale are needed. Seventh, the use of sulfonylureas was not added to the covariates. When sulfonylureas, especially glibenclamide, are used by older adults, adverse events are known to reduce compliance (34). However, the population of our study is characterized by a large number of subjects in their 30s and 50s and few elderly people. Eighth, by analyzing the risk of developing diabetes on the basis of time-varying coefficient models and dose-response relationships, we can obtain more detailed knowledge about risk. In our study, the sample size was small and additional analysis was difficult. In the future, more detailed research would be desirable. Ninth, it is important to know whether sex and age have different effects on changes in HbA_{1c} level after antidepressant withdrawal. In addition, HbA_{1c} level before antidepressant withdrawal might affect the improvement in glucose tolerance after withdrawal. However, our sample size was small and the results could not be generalized. Regarding the follow-up of HbA_{1c}, it is desirable to analyze by drug class at the HbA_{1c} level. Finally, because medical claims data are issued monthly, there may be discrepancies between actual medications administered and medications prescribed. Nevertheless, this study is clinically important because we analyzed a large Japanese population (3.4 million individuals) insured by employee health insurance associations.

Conclusion

Long-term antidepressant use might increase the risk of type 2 diabetes in a time- and dose-dependent manner. Moreover, discontinuation of antidepressant therapy and reduction of the antidepressant dose after type 2 diabetes onset improved glucose tolerance. Accordingly, HbA_{1c} level should be regularly monitored in patients taking antidepressants in order to inform the decision to reduce or discontinue antidepressant use, if possible, when impaired glucose tolerance is observed.

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