Antidiabetes Agents and Incident Depression: A Nationwide Population-Based Study

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OBJECTIVE

Diabetes is associated with an increased risk of depression. Some antidiabetes agents, specifically metformin and pioglitazone, have been suggested to have beneficial effects on depression, but associations between antidiabetes drugs and depression have not been systematically investigated.

RESEARCH DESIGN AND METHODS

We combined four Danish population-based registers to investigate whether the 20 most widely used orally administered antidiabetes drugs were associated with an altered risk of incident depression. Analyses of insulin were included for comparisons. All persons in Denmark in 2005 were included in the study and followed until 2015. Two different outcome measures of incident depression were included: *1*) a diagnosis of depressive disorder at a psychiatric hospital as an inpatient or outpatient and *2*) a combined measure of a diagnosis of depression or use of antidepressants. Data were analyzed using Cox regression models.

RESULTS

A total of 360,205 individuals using orally administered antidiabetes drugs and 64,582 using insulin at any time during the study period were included in the analyses. Continued use of metformin and combinations of drugs including metformin were associated with decreased rates of incident depression. Pioglitazone was not associated with a decreased rate of incident depression. No other antidiabetes drugs or insulin showed significant associations with depression.

CONCLUSIONS

Real-life population-based data suggest a positive effect of metformin on depression rates. This evidence should be used in guiding prescriptions for patients with type 2 diabetes who are at risk for developing depression, including those with prior depression or anxiety and patients with a family history of depression.

People with type 2 diabetes are more likely to develop depressive symptoms (1), and people with depression are more likely to develop type 2 diabetes (2). Depression comorbid with diabetes impairs quality of life and is associated with less effective self-management, a higher risk of diabetes complications (3), and higher rates of cardiovascular mortality as well as all-cause mortality (4). There is an overlap in biological pathways between type 2 diabetes and depression. Firstly, there seems to be a genetic overlap between risk for type 2 diabetes and depression (5). Secondly, increased circulating inflammatory markers are seen in patients with depressive symptoms and type 2 diabetes compared with patients with type 2 diabetes alone

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(6–8). Thirdly, insulin resistance is a core pathophysiologic trait of type 2 diabetes and is consistently associated with depressive symptoms (6,9). Also, the two disorders share many lifestyle and environmental risk factors such as diet and physical activity (10,11). Finally, hyperglycemia seems to be associated with depressive symptoms (6).

Antidiabetes drugs improve glycemic control via a diverse range of effects including amelioration of insulin resistance, stimulation of insulin secretion, and suppression of glucagon secretion. Some antidiabetes drugs have also been shown to reduce the low-grade inflammation associated with obesity and type 2 diabetes, while conventional antidepressants have not shown consistent effects on these parameters (6). Many antidiabetes drugs, including metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, and thiazolidinediones, may cross the blood-brain barrier (6), and, in particular, metformin has shown neuroactive effects on depression-related pathways such as neurotrophins and axonal regeneration (12) besides its anti-inflammatory, antiapoptotic, and antioxidant properties (13,14). However, clinical data evaluating the effect of diabetes drugs on depression remain scarce. In a meta-analysis, pioglitazone was the only antidiabetes drug associated with improvement in depressive symptoms, although metformin was nonsignificantly superior to placebo, whereas the GLP-1 receptor agonist, liraglutide, and insulin showed no effects (6). Importantly, few of the studies included in the meta-analysis were designed to test the hypothesis that a given antidiabetes drug improves or prevents depression. In relation to metformin, only one study by Guo et al. (15) showing a positive effect on depression was specifically designed to investigate the effect of metformin versus placebo. Also, the randomized controlled trials (RCTs) included were mainly based on small sample sizes of between 8 and 100 patients (6), and the quality of the studies varied substantially, mainly being based on modeling and pilot data, of which several tested depressive symptoms as a secondary outcome. Finally, the included populations were highly heterogeneous including patients with diabetes and post-stroke depression (16), polycystic ovarian syndrome (17,18), Parkinson disease (19), overweight (20), metabolic syndrome (21), and bipolar depression (22,23). Only one trial included patients with type 2 diabetes as the main recruiting criteria (15).

In the Register Wise Association Study (R-WAS), we used Danish nationwide population-based registers to investigate whether agents with an a priori preclinical or theoretical evidence base may have effects in depression (24). This approach is based on a theoretical construct: that of shared environmental risks as well as common biological pathways for diverse noncommunicable disorders, including depression, cardiovascular disorders, and diabetes (25). Here, we report the effects of antidiabetes drugs on risk of incident depression as part of R-WAS.

Aims of the Study

We used Danish population-based registers to systematically investigate whether orally administered antidiabetes drugs are associated with altered rate of incident depression. Analyses of insulin were included for comparisons. To take into account confounding by indication, we estimated the rate of incident depression during successive prescription periods of the drugs (periods 1–2, 3–5, 6–10, and >10), whereas the period with nonuse was included for comparison (see below).

Hypotheses

Due to the overlapping biological pathways involved in the pathogenesis and treatment mechanisms of type 2 diabetes and depression, we hypothesized that continued use of treatments for type 2 diabetes overall decreases the rate of incident depression and that the rates decrease with the number of prescriptions. Based on prior studies, including the study by Guo et al. (15) and the systematic review and meta-analysis by Moulton et al. (6), we hypothesized that metformin, including combination drugs of metformin, and secondly pioglitazone would be associated with a decreased rate of depression. On the other hand, we did not expect effects of insulin, as the pathogenesis of type 1 diabetes and treatment mechanisms differ from those of depression.

RESEARCH DESIGN AND METHODS

The Registers Used

Data were obtained by linking of Danish population-based registers using the unique personal identification number assigned to all 5.7 million persons living in Denmark, thus ensuring accurate linkage of information between registers, irrespective of changes in name and demographics (26). In this way, the Register of Medicinal Product Statistics (27) was linked with the Danish Medical Register on Vital Statistics (28), the Danish National Hospital Register (29), and the Danish Psychiatric Central Register (30). The Register of Medicinal Product Statistics contains data on all prescribed medication purchased at pharmacies from 1 January 1995 and onward (27). The register includes prescription data from all physicians in Denmark, i.e., from primary care including general practice and private specialists and from secondary outpatient hospital care settings. The Danish Medical Register on Vital Statistics (28) contains data on deaths. The Danish National Hospital Register (29) contains data on all patients treated at all somatic hospitals as inpatients or outpatients in Denmark from 1 January 1977 onward as a part of the official Danish health survey (31). Likewise, all psychiatric admissions and diagnoses are recorded in the register (as part of the Danish Psychiatric Central Register [30]) from 1 April 1970 onward. Since 1 January 1994 the ICD-10 has been in use in both registers (31), and since 1 January 1995 diagnoses from outpatient contacts have been included. Diagnoses from primary care are not included in the registers, but pharmacological treatment from primary care is recorded in the Danish Medical Register on Vital Statistics (as prescriptions from all other physicians).

Drug Identification

Drugs were identified according to the Anatomical Therapeutic Chemical (ATC) Classification System as defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology (32).

Study Population

All 5.4 million individuals in Denmark were included in the study in January 2005. The following individuals were excluded: *1*) individuals who purchased antidepressants at least once between the start of the medical register in 1995 and the start of our study period (1 January 2005) and *2*) individuals with a diagnosis of depression (back to 1970) prior to entry into the study.

Outcome Measures

The primary outcome measure was a diagnosis of depressive disorder (ICD

codes DF32–DF33.31) given at a psychiatric contact (as inpatient or outpatient) and as identified in the Danish Psychiatric Central Register. A secondary outcome measure was defined as a combined end point of either the primary outcome or use of antidepressants (ATC: N06A).

Follow-up Period

Individuals were followed from entry into the study until date of death; date of a diagnosis of organic mental disorders, mental disorders due to psychoactive substance use, schizophrenia, and mania/bipolar disorder (DF00-31.9 included); or 31 December 2015 (end of study period)—whatever came first.

Exposure Drugs

Exposures included all medications approved for the treatment of type 2 diabetes. In addition, a total of 20 of the most prescribed medications for type 2 diabetes were investigated separately (see list in Table 1).

Comorbidity

Somatic diagnoses were categorized within nine ICD-8– and ICD-10–defined somatic disease chapters (I, infections; II, neoplasms; III, diseases of the blood; IV, IX, and X, endocrine, nutritional, and metabolic diseases and diseases of the circulatory or respiratory system; VI–VIII, diseases of the nervous system, eye, and ear; XI, diseases of the digestive system; XII, diseases of the skin and subcutaneous tissue; XIII, diseases of the musculoskeletal system; and XIV, diseases of the genitourinary system and pregnancy, childbirth, and the puerperium) and separately within each of these disease areas.

Design of the Analyses

There are two main potential sources of errors in the planned analyses that we proactively addressed: Confounding by indication may occur if an unobserved variable (e.g., diabetes) is a risk factor for the studied outcome (depression) and at the same time is an indication of the drug of interest (33). Detection bias may occur if subjects who are prescribed antidiabetes drugs are more likely to be diagnosed with the outcome disease (depression) or to go on antidepressants than subjects unexposed to antidiabetes drugs. However, strategic sampling designs may be worked out as previously done in pharmaco-epidemiological studies by our group (34,35). To control for confounding effects and detection bias and to estimate the effect of duration of treatment, we compared rates during successive prescriptions of the exposure drug as in prior studies (34,35). In this way, the cumulative number of redeemed antidiabetes drug prescriptions was the exposure and incidence of depression the outcome. Particularly, we used one to two prescriptions as our reference group and thereby only compared users of a drug with other users of the same drug. Prescription group 0 (control group) was included only to illustrate confounding by indication.

Statistical Analyses

The association between drug exposure and the rate of incident depression was analyzed separately for each drug using Cox regression with time-dependent exposure as defined below. We fitted these models using a nested case-control design (36,37) with 10 age- and sex-matched individuals of the control group (referred to here as control subjects) for each individual with depression (case subjects). The nested case-control design is a computationally efficient alternative to the cohort design for fitting a Cox regression model with time-dependent exposure (37). In these analyses, each follow-up day where a subject is at risk for experiencing the outcome is categorized according to the current values of the drug exposure and of the potential confounders at the start of the exposure window whereby the daily risk (the rate) of the outcome can be ascertained. The drug exposure on a given day during follow-up was defined as the cumulated number of prescriptions of the candidate drug during the last 10 years in appropriate categories (number and width of categories were chosen depending on the general usage of the candidate drug). The category "one to two prescriptions" was used as the reference category in all analyses. The exposure category was evaluated for each case subject and the corresponding matched control subjects on the case subject's date of depression diagnosis. To note the cumulation of exposure in the fixed 10-year period, we restricted all analyses of the outcomes to the period 2005–2015 (the Danish Medical Product Statistics register starts in 1995). Separate analyses were performed for the different diabetes treatments. Separate analyses were done with the combined end point (incident depression or use of antidepressants) as the outcome measure. All analyses were matched for current age, sex, and current calendar year and adjusted for additive effects of current employment status (working or student = reference, unemployed, age, pension, disability, other) (partially adjusted analyses). Additional analyses were performed in which we adjusted for additive effects of the time-dependent comorbidity status with additive effects of nine dummy variables indicating the nine comorbidity groups listed in the section COMORBIDITY (fully adjusted analyses). The comorbidity status was always evaluated 10 years previously to avoid time interference between exposure status and comorbidity. Hazard ratios (HRs) with 95% confidence limits and exposure trend tests obtained were reported with a likelihood ratio test comparing a Cox regression model without drug exposure to a model that assumes a linear increase in outcome hazard rate between the exposure categories (excluding the nonuse category). Data are reported for all antidiabetes drugs combined and insulin (Table 2) and for the 20 most prescribed individual antidiabetes drugs (Table 3). Due to multiple testing in relation to individual drugs, we Bonferroni-adjusted *P* values for the number of drugs in the analyses (20 drugs). To be considered statistically significant, *P* values should be less than $P < 0.003$ for the individual drug.

All analyses were performed with R (38).

Statement of Ethics

Ethics approval of anonymous register studies is not needed according to Danish law. Regarding data approval, the study was approved by the Data Agency of the Capital Region of Denmark.

RESULTS

A total of 360,205 subjects were exposed to 1 of the 20 antidiabetes drugs, and 64,582 were exposed to insulin during the exposure period from 2005 to 2015. Table 1 shows the number of subjects exposed in total and for each drug (*N*) as well as age and female sex proportion at first prescription. Notably, 283,741 individuals were exposed to metformin, while 1,210 were exposed to pioglitazone.

Table 2 presents HRs according to prescription number of all antidiabetes drugs combined and insulin, respectively,

Table 1—Number of individuals exposed in total and for each drug during the exposure period 2005–2015, age, and female sex proportion at date of first prescription

Drug	*N*	Age, median (quartiles)	% female
Antidiabetes agents, all	360,205	61 (50, 71)	46
Insulin, all	64,582	55 (38, 68)	43
A10BA02, metformin	283,741	62 (51, 71)	47
A10BB01, glibenclamide	13,423	68 (59, 77)	44
A10BB03, tolbutamide	4,291	71 (61, 80)	44
A10BB07, glipizide	8,715	68 (60, 78)	45
A10BB09, gliclazide	15,086	66 (57, 75)	42
A10BB12, glimepiride	92,957	65 (56, 74)	43
A10BD03, metformin and rosiglitazone	5,865	61 (54, 69)	41
A10BD07, metformin and sitagliptin	14,049	62 (54, 70)	39
A10BD08, metformin and vildagliptin	14,262	63 (54, 70)	38
A10BF01, acarbose	1,651	66 (57, 76)	48
A10BG02, rosiglitazone	2,546	62 (55, 71)	44
A10BG03, pioglitazone	1,210	61 (52, 69)	44
A10BH01, sitagliptin	28,602	63 (55, 71)	42
A10BH02, vildagliptin	5,409	66 (57, 74)	43
A10BH03, saxagliptin	2,812	65 (56, 72)	43
A10BH05, linagliptin	5,191	72 (64, 80)	42
A10BX02, repaglinide	3,903	64 (56, 74)	43
A10BX04, exenatide	2,864	57 (48, 63)	44
A10BX07, liraglutide	31,723	59 (50, 66)	43
A10BX09, dapagliflozin	7,619	60 (52, 68)	39

with adjustment for age, sex, employment status, and calendar year (partially adjusted) and additionally adjustment for somatic diagnoses (fully adjusted) and trend tests. Results of analyses for which the outcome measure was a "diagnosis of depression" are at the left side of the table, whereas results from analyses with a diagnosis of depression or use of antidepressants as the outcome measure are shown on the right side of the table. As can be seen, for both orally administered antidiabetes agents and insulin, the hazard rate of depression and the hazard rate of depression or use of antidepressants, respectively, were significantly lower in subjects with 0 prescriptions (nonuse of antidiabetes drugs) compared with one to two prescriptions, reflecting that patients with diabetes may be at increased risk of developing depression. For orally administered antidiabetes agents as a class, hazard rates were decreased during prescription periods 3–5, 6–10, and >10, respectively, compared with the reference period 1–2 in the two analyses with a "diagnosis of depression" as the outcome measure, i.e., in analyses partially adjusted (trend test HR 0.95 [95% CI 0.92–0.97], $P < 0.001$) and fully adjusted including somatic diagnoses (trend test HR 0.94 [95% CI 0.91–0.97], $P < 0.001$).

Table 3 shows results for the 20 most prescribed individual orally administered antidiabetes drugs. Individual drugs are highlighted for which statistically significant associations with incident depression were found in all four analyses, i.e., analyses with a "diagnosis of depression" and a "diagnosis of depression or use of antidepressant" as the outcome measures, respectively, and partially and fully adjusted, respectively. Across all four analyses, metformin and the combination of metformin with vildagliptin (a dipeptidyl peptidase 4 inhibitor) were associated with decreased rates of incident depression according to trend tests. All of these analyses survived Bonferroni correction, with $P < 0.001$ for all except in one analysis for metformin ($P = 0.004$). Further, the combination of metformin and sitagliptin (also a dipeptidyl peptidase 4 inhibitor) was associated with decreased rates of depression in the two analyses with the combined outcome measure of a diagnosis of depression or use of antidepressants (unadjusted and adjusted for somatic diagnoses) but not in analyses with depression diagnosis as the outcome. Pioglitazone was not associated with a decreased rate of depression in any of the four analyses. In fact, rate ratios of pioglitazone were increased in analyses with a diagnosis of depression as the outcome measure, but the *P* value survived Bonferroni correction only in the fully adjusted analysis (HR 2.08 [95% CI 1.30–3.34], $P = 0.002$)

CONCLUSIONS

This is the first study based on population-based health data to investigate the association between use of antidiabetes drugs and depression. Using Danish nationwide population-based registers, we demonstrate that continued use of metformin and combinations of metformin with other antidiabetes drugs were associated with decreased rates of depression, whereas, in contrast to some previous findings, pioglitazone was not associated with a decreased rate of depression. No other antidiabetes drug showed effects on incident depression.

Strengths of the Study

The current study has several strengths. Firstly, the study is a systematic investigation of all persons in Denmark, ~360,000, who used the 20 most prescribed orally administered antidiabetes drugs and all persons, ~64,582, who used insulin over a study period of 10 years. More than 280,000 patients were included in the analyses of metformin alone. Secondly, our data support the validity of the R-WAS methodology, as we detected the hypothesized positive effect of metformin out of the 20 investigated orally administered antidiabetes drugs. It is clear from Table 3 that findings for the individual drugs vary a lot, with some showing increased, some decreased, and some no association with incident depression, excluding that they are a result of systematic or general bias or confounding. If the findings were just a general result of the design of the study, we may not only have confirmed our main hypothesis showing an effect of metformin and metformin combinations but may have found similar results for other drugs. Thus, in the prespecified plan of analyses, we decided to address bias and confounding by indication of antidiabetes agents in two different

Table 2—Prescription number of orally administered antidiabetes drugs and insulin, HRs of "diagnosis of depression" and "diagnosis of depression or use of antidepressant," respectively, and trend tests

		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Drug	Prescription number	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test
Noninsulin antidiabetes agents	1–2	1.00	**0.95 (0.92–0.97), $P < 0.001$**	1.00	**0.94 (0.91–0.97), $P < 0.001$**	1.00	0.99 (0.97–1.01), $P = 0.4$	1.00	0.99 (0.97–1.01), $P = 0.4$
	0	0.57 (0.53–0.62)		0.69 (0.63–0.75)		0.67 (0.63–0.71)		0.72 (0.68–0.77)	
	3–5	0.90 (0.79–1.03)		0.90 (0.78–1.03)		0.89 (0.81–0.98)		0.88 (0.79–0.97)	
	6–10	0.77 (0.68–0.88)		0.75 (0.66–0.86)		0.90 (0.82–0.98)		0.90 (0.82–0.99)	
	>10	0.83 (0.75–0.90)		0.81 (0.73–0.88)		0.94 (0.87–1.00)		0.93 (0.87–1.00)	
Insulin	1–2	1.00	1.00 (0.95–1.05), $P = 0.9$	1.00	1.01 (0.95–1.06), $P = 0.8$	1.00	1.00 (0.95–1.05), $P = 0.9$	1.00	1.01 (0.95–1.06), $P = 0.8$
	0	0.59 (0.51–0.68)		0.76 (0.66–0.87)		0.59 (0.51–0.68)		0.76 (0.66–0.87)	
	3–5	0.90 (0.69–1.17)		0.85 (0.64–1.11)		0.90 (0.69–1.17)		0.85 (0.64–1.11)	
	6–10	1.06 (0.82–1.38)		0.99 (0.76–1.30)		1.06 (0.82–1.38)		0.99 (0.76–1.30)	
	>10	0.97 (0.83–1.14)		0.99 (0.84–1.17)		0.97 (0.83–1.14)		0.99 (0.84–1.17)	

Adjustment for age, sex, employment status, and calendar year (partially adjusted) and additional adjustment for somatic diagnoses (fully adjusted). Statistically significant trend tests are highlighted in boldface type.

ways: *1*) the design of the study and *2*) the adjustment methods. *1*) The study was designed to estimate the rate of incident depression during successive prescription periods of the drug compared with the rate during prescription period 1–2. We generally confirmed that the prescription period 1–2 (i.e., start of an antidiabetes drug) was associated with increased HR of depression compared with the nonuse period (i.e., no exposure to an antidiabetes drug) (Table 3), suggesting confounding by indication, since drugs were prescribed for diabetes that are associated with increased risk of depression (1). *2*) In addition to adjusting for sex, age, employment status, and calendar period, we adjusted the analyses for all physical comorbidities recorded in the Danish National Hospital Register, as many patients suffer from multiple diseases (e.g., co-occurrence of diabetes with cardiovascular disease or chronic pain [39]), aiming to reduce unknown or residual confounding. Thirdly, two different outcome measures were included: a diagnosis of depressive disorder at a psychiatric hospital contact as inpatient or outpatient and a combined measure of a diagnosis of depression or antidepressant use. Notably, the study includes prescription data from all physicians in Denmark, i.e., from primary care including general practice and private specialists and from secondary outpatient hospital care. In most analyses, the results with the two outcome measures were similar, serving to increase the internal and external validity of the findings. Fourthly, potential reverse causation is minimized, as only incident depression and use of antidepressants were included in the analyses, since we excluded individuals who received antidepressants (from 1995 to 2005) or had a diagnosis of depression (back to 1970) prior to the drug class of interest. Finally, population-based data such as those included in the current study reflect real life, with so-called naturalistic data adding to increase the generalizability of findings. By contrast, a large proportion of real-life patients are excluded from RCTs due to the strict inclusion and exclusion criteria often deployed. Among patients with depression in clinical practice, up to one-third meet usual eligibility requirements for an antidepressant efficacy trial.

Although results of trend tests for HRs of metformin were between 0.93 and 0.97, these are considered clinically meaningful. Firstly, the trend tests reflect long-term associations, and secondly, during the individual prescription periods, associations were stronger, with HR varying between 0.56 and 0.93. The relationship between metformin and decreased rate of incident depression does not seem to be due to the largest number of patients being on metformin, as statistical power was high for other antidiabetes drugs as well, as illustrated by the narrow CIs of these HRs.

Limitations of the Study

The current study also has some limitations. The primary outcome measure was not research based but was based on clinical diagnoses. However, the ICD-10 diagnosis of depression recorded in the Danish Psychiatric Central Research Register has a high validity as compared with a research diagnostic interview with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (40).

Table 3—Prescription number of orally administered antidiabetes drugs, HR of "diagnosis of depression" and "diagnosis of depression or use of antidepressant," respectively, and trend tests

		Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
Drug	Prescription number	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test
Metformin	1–2	1.00	**0.93 (0.91–0.96), $P < 0.001$**	1.00	**0.93 (0.90–0.96), $P < 0.001$**	1.00	**0.97 (0.95–0.99), $P = 0.001$**	1.00	**0.97 (0.95–0.99), $P = 0.004$**
	0	0.56 (0.51–0.61)		0.67 (0.62–0.73)		0.59 (0.55–0.62)		0.65 (0.61–0.69)	
	3–5	0.89 (0.78–1.02)		0.88 (0.77–1.01)		0.85 (0.77–0.93)		0.85 (0.77–0.93)	
	6–10	0.93 (0.82–1.06)		0.91 (0.80–1.03)		0.84 (0.76–0.91)		0.84 (0.77–0.92)	
	>10	0.81 (0.73–0.89)		0.79 (0.71–0.87)		0.87 (0.81–0.93)		0.87 (0.81–0.93)	
Glibenclamide	1–2	1.00	**0.88 (0.80–0.96), $P = 0.003$**	1.00	**0.91 (0.83–0.99), $P = 0.035$**	1.00	1.03 (0.97–1.09), $P = 0.357$	1.00	1.03 (0.97–1.09), $P = 0.405$
	0	0.62 (0.50–0.78)		0.80 (0.64–1.00)		0.74 (0.63–0.86)		0.78 (0.67–0.92)	
	3–5	0.70 (0.47–1.02)		0.75 (0.51–1.12)		0.56 (0.42–0.75)		0.55 (0.41–0.75)	
	6–10	0.61 (0.42–0.90)		0.67 (0.46–0.98)		0.72 (0.56–0.92)		0.71 (0.55–0.91)	
	>10	0.64 (0.49–0.83)		0.72 (0.55–0.94)		0.93 (0.78–1.12)		0.93 (0.77–1.11)	
Tolbutamide	1–2	1.00	1.05 (0.91–1.22), $P = 0.464$	1.00	1.06 (0.92–1.22), $P = 0.437$	1.00	0.94 (0.86–1.03), $P = 0.208$	1.00	0.94 (0.86–1.03), $P = 0.198$
	0	0.79 (0.55–1.15)		0.86 (0.59–1.25)		0.69 (0.55–0.87)		0.74 (0.59–0.93)	
	3–5	0.73 (0.38–1.39)		0.70 (0.37–1.36)		0.65 (0.44–0.97)		0.68 (0.45–1.01)	
	6–10	0.95 (0.52–1.74)		0.87 (0.48–1.57)		0.78 (0.54–1.13)		0.78 (0.54–1.13)	
	>10	1.07 (0.70–1.66)		1.08 (0.70–1.66)		0.77 (0.58–1.01)		0.77 (0.58–1.02)	
Glipizide	1–2	1.00	1.01 (0.89–1.14), $P = 0.888$	1.00	1.04 (0.92–1.17), $P = 0.560$	1.00	**1.17 (1.08–1.26), $P < 0.001$**	1.00	**1.19 (1.09–1.28), $P < 0.001$**
	0	0.75 (0.54–1.05)		0.89 (0.64–1.25)		1.18 (0.92–1.52)		1.31 (1.02–1.68)	
	3–5	0.76 (0.44–1.31)		0.72 (0.42–1.22)		1.36 (0.94–1.96)		1.41 (0.97–2.04)	
	6–10	0.74 (0.44–1.25)		0.76 (0.46–1.27)		1.47 (1.05–2.08)		1.57 (1.12–2.20)	
	>10	0.94 (0.64–1.37)		0.99 (0.68–1.45)		1.67 (1.26–2.20)		1.77 (1.35–2.32)	
Gliclazide	1–2	1.00	1.08 (0.96–1.21), $P = 0.194$	1.00	1.10 (0.97–1.23), $P = 0.136$	1.00	1.04 (0.97–1.12), $P = 0.287$	1.00	1.05 (0.97–1.13), $P = 0.210$
	0	1.02 (0.71–1.47)		1.25 (0.85–1.83)		0.79 (0.63–0.99)		0.86 (0.68–1.07)	
	3–5	1.63 (1.01–2.62)		1.74 (1.06–2.85)		1.10 (0.79–1.54)		1.09 (0.78–1.53)	
	6–10	1.01 (0.60–1.72)		1.06 (0.62–1.82)		1.19 (0.86–1.63)		1.16 (0.84–1.60)	
	>10	1.45 (0.97–2.16)		1.54 (1.01–2.35)		1.15 (0.90–1.48)		1.17 (0.91–1.51)	
Glimepiride	1–2	1.00	**0.90 (0.86–0.94), $P < 0.001$**	1.00	**0.91 (0.87–0.96), $P < 0.001$**	1.00	1.01 (0.98–1.04), $P = 0.410$	1.00	1.02 (0.99–1.05), $P = 0.231$
	0	0.55 (0.49–0.62)		0.68 (0.60–0.77)		0.69 (0.63–0.75)		0.76 (0.69–0.83)	
	3–5	0.89 (0.74–1.08)		0.89 (0.73–1.07)		1.10 (0.97–1.25)		1.09 (0.95–1.24)	
	6–10	0.73 (0.61–0.88)		0.73 (0.60–0.88)		0.98 (0.87–1.11)		0.97 (0.86–1.10)	
	>10	0.72 (0.63–0.84)		0.76 (0.65–0.88)		1.06 (0.96–1.17)		1.08 (0.97–1.19)	

Continued on p. 3056

Table 3—Continued

Drug	Prescription number	Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
		HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test
Metformin + rosiglitazone	1–2	1.00	0.99 (0.82–1.20), $P = 0.929$	1.00	1.02 (0.84–1.24), $P = 0.825$	1.00	0.91 (0.81–1.01), $P = 0.088$	1.00	**0.89 (0.79–0.99), $P = 0.039$**
	0	1.09 (0.59–2.01)		1.49 (0.84–2.64)		0.51 (0.38–0.68)		0.53 (0.39–0.71)	
	3–5	1.96 (0.85–4.54)		1.73 (0.72–4.11)		0.79 (0.49–1.29)		0.74 (0.45–1.22)	
	6–10	1.40 (0.58–3.37)		1.46 (0.64–3.30)		1.03 (0.68–1.57)		0.90 (0.58–1.38)	
	>10	1.20 (0.59–2.42)		1.26 (0.65–2.46)		0.72 (0.51–1.02)		0.66 (0.46–0.95)	
Metformin + sitagliptin	1–2	1.00	0.96 (0.77–1.20), $P = 0.729$	1.00	0.99 (0.78–1.26), $P = 0.948$	1.00	**0.75 (0.65–0.86), $P < 0.001$**	1.00	**0.75 (0.65–0.87), $P < 0.001$**
	0	0.50 (0.31–0.80)		0.71 (0.44–1.17)		0.38 (0.29–0.49)		0.42 (0.32–0.55)	
	3–5	0.64 (0.30–1.40)		0.67 (0.31–1.45)		0.38 (0.22–0.64)		0.38 (0.22–0.65)	
	6–10	0.71 (0.35–1.46)		0.74 (0.34–1.63)		0.63 (0.40–0.98)		0.63 (0.40–0.98)	
	>10	0.85 (0.45–1.62)		0.94 (0.47–1.87)		0.36 (0.23–0.56)		0.37 (0.24–0.58)	
Metformin + vildagliptin	1–2	1.00	**0.68 (0.56–0.83), $P < 0.001$**	1.00	**0.69 (0.55–0.86), $P < 0.001$**	1.00	**0.80 (0.71–0.92), $P = 0.001$**	1.00	**0.80 (0.70–0.92), $P = 0.001$**
	0	0.42 (0.28–0.63)		0.52 (0.34–0.79)		0.45 (0.34–0.60)		0.52 (0.38–0.69)	
	3–5	0.93 (0.51–1.69)		0.84 (0.44–1.59)		0.89 (0.57–1.39)		0.93 (0.59–1.47)	
	6–10	0.56 (0.28–1.13)		0.59 (0.29–1.19)		0.62 (0.39–1.00)		0.66 (0.41–1.06)	
	>10	0.30 (0.15–0.61)		0.31 (0.15–0.66)		0.54 (0.36–0.81)		0.53 (0.35–0.81)	
Acarbose	1–2	1.00	**1.28 (1.01–1.62), $P = 0.042$**	1.00	1.27 (1.00–1.62), $P = 0.052$	1.00	**0.82 (0.72–0.94), $P = 0.003$**	1.00	**0.81 (0.71–0.92), $P = 0.001$**
	0	2.02 (0.91–4.50)		2.43 (1.08–5.46)		0.53 (0.40–0.69)		0.56 (0.43–0.74)	
	3–5	2.64 (0.92–7.63)		2.58 (0.87–7.63)		0.64 (0.37–1.11)		0.66 (0.38–1.15)	
	6–10	2.74 (0.95–7.92)		2.90 (0.96–8.78)		0.76 (0.45–1.25)		0.77 (0.46–1.28)	
	>10	2.63 (1.06–6.52)		2.57 (1.02–6.47)		0.52 (0.35–0.79)		0.50 (0.33–0.75)	
Rosiglitazone	1–2	1.00	0.94 (0.74–1.20), $P = 0.632$	1.00	0.98 (0.76–1.28), $P = 0.908$	1.00	0.84 (0.70–1.02), $P = 0.072$	1.00	0.87 (0.72–1.04), $P = 0.131$
	0	0.44 (0.26–0.77)		0.60 (0.34–1.05)		0.50 (0.35–0.72)		0.59 (0.42–0.84)	
	3–5	0.65 (0.26–1.64)		0.76 (0.31–1.88)		0.35 (0.16–0.75)		0.37 (0.17–0.81)	
	6–10	0.92 (0.41–2.07)		0.79 (0.35–1.75)		0.99 (0.59–1.69)		1.06 (0.63–1.79)	
	>10	0.76 (0.36–1.61)		0.93 (0.43–2.03)		0.43 (0.23–0.81)		0.48 (0.26–0.88)	
Pioglitazone	1–2	1.00	**1.88 (1.20–2.95), $P = 0.006$**	1.00	**2.08 (1.30–3.34), $P = 0.002$**	1.00	1.20 (0.99–1.46), $P = 0.061$	1.00	**1.22 (1.00–1.48), $P = 0.049$**
	0	6.11 (0.86–43.31)		7.35 (1.03–52.60)		0.63 (0.40–0.99)		0.65 (0.41–1.02)	
	3–5	4.41 (0.40–48.52)		3.80 (0.34–43.00)		1.41 (0.71–2.81)		1.16 (0.58–2.32)	
	6–10	9.17 (1.02–82.04)		10.04 (1.18–85.23)		0.71 (0.31–1.59)		0.70 (0.32–1.55)	

Continued on p. 3057

Table 3—Continued

Drug	Prescription number	Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
		HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test
Sitagliptin	1–2	1.00	0.91 (0.79–1.03), $P = 0.136$	1.00	0.93 (0.82–1.07), $P = 0.302$	1.00	1.05 (0.97–1.15), $P = 0.214$	1.00	1.06 (0.97–1.15), $P = 0.186$
	0	0.51 (0.39–0.66)		0.63 (0.48–0.82)		0.81 (0.66–0.99)		0.91 (0.74–1.11)	
	3–5	0.72 (0.48–1.10)		0.75 (0.49–1.14)		1.37 (1.02–1.83)		1.39 (1.04–1.87)	
	6–10	0.78 (0.51–1.18)		0.80 (0.52–1.23)		1.33 (1.00–1.77)		1.38 (1.03–1.84)	
	>10	0.72 (0.48–1.07)		0.79 (0.53–1.19)		1.20 (0.91–1.59)		1.21 (0.92–1.61)	
Vildagliptin	1–2	1.00	1.11 (0.72–1.73), $P = 0.629$	1.00	1.20 (0.78–1.84), $P = 0.398$	1.00	0.88 (0.71–1.10), $P = 0.263$	1.00	0.86 (0.68–1.07), $P = 0.181$
	0	1.11 (0.42–2.96)		1.50 (0.60–3.74)		0.53 (0.33–0.86)		0.59 (0.36–0.98)	
	3–5	1.48 (0.37–5.93)		1.60 (0.44–5.85)		1.30 (0.65–2.59)		1.45 (0.71–2.98)	
	6–10	1.38 (0.34–5.52)		1.67 (0.46–6.04)		1.44 (0.70–2.94)		1.31 (0.62–2.75)	
	>10	1.43 (0.32–6.34)		1.76 (0.40–7.72)		0.56 (0.25–1.29)		0.54 (0.23–1.26)	
Saxagliptin	1–2	1.00	0.67 (0.39–1.14), $P = 0.140$	1.00	0.69 (0.41–1.14), $P = 0.147$	1.00	0.92 (0.68–1.24), $P = 0.565$	1.00	0.90 (0.67–1.0020), $P = 0.480$
	0	0.38 (0.18–0.81)		0.54 (0.25–1.18)		0.46 (0.26–0.81)		0.52 (0.29–0.93)	
	3–5	0.19 (0.02–1.55)		0.25 (0.03–2.19)		0.74 (0.31–1.79)		0.84 (0.34–2.10)	
	6–10	0.43 (0.11–1.67)		0.49 (0.12–2.03)		0.43 (0.17–1.13)		0.44 (0.17–1.12)	
	>10	0.30 (0.06–1.44)		0.30 (0.06–1.48)		0.91 (0.40–2.10)		0.88 (0.39–2.02)	
Linagliptin	1–2	1.00	0.79 (0.45–1.36), $P = 0.388$	1.00	0.80 (0.45–1.42), $P = 0.447$	1.00	1.16 (0.85–1.59), $P = 0.346$	1.00	1.18 (0.86–1.62), $P = 0.311$
	0	0.50 (0.19–1.35)		0.55 (0.19–1.58)		0.53 (0.29–0.97)		0.57 (0.30–1.06)	
	3–5	2.83 (0.71–11.20)		3.00 (0.77–11.66)		0.70 (0.26–1.90)		0.71 (0.27–1.91)	
	6–10	0.77 (0.14–4.23)		0.97 (0.17–5.64)		1.14 (0.45–2.86)		1.21 (0.48–3.06)	
	>10	0.00 (0.00–0.00)		0.00 (0.00–0.00)		1.49 (0.59–3.79)		1.53 (0.59–3.98)	
Repaglinide	1–2	1.00	0.97 (0.83–1.13), $P = 0.688$	1.00	0.99 (0.85–1.16), $P = 0.894$	1.00	0.99 (0.90–1.09), $P = 0.847$	1.00	0.98 (0.89–1.08), $P = 0.708$
	0	0.71 (0.46–1.08)		0.85 (0.56–1.28)		0.63 (0.48–0.83)		0.68 (0.51–0.91)	
	3–5	0.83 (0.39–1.75)		0.90 (0.43–1.89)		1.55 (1.02–2.36)		1.69 (1.09–2.61)	
	6–10	1.72 (0.93–3.18)		1.85 (1.00–3.43)		0.97 (0.61–1.55)		0.98 (0.61–1.59)	
	>10	0.87 (0.52–1.45)		0.94 (0.56–1.56)		1.08 (0.79–1.49)		1.07 (0.77–1.49)	
Exenatide	1–2	1.00	1.02 (0.78–1.33), $P = 0.894$	1.00	1.08 (0.80–1.45), $P = 0.624$	1.00	0.88 (0.72–1.07), $P = 0.205$	1.00	0.93 (0.75–1.15), $P = 0.503$
	0	0.52 (0.27–1.00)		0.80 (0.37–1.72)		0.34 (0.20–0.58)		0.43 (0.24–0.76)	
	3–5	1.24 (0.48–3.15)		1.34 (0.49–3.71)		0.89 (0.43–1.84)		1.00 (0.46–2.19)	
	6–10	0.85 (0.30–2.41)		0.91 (0.31–2.68)		0.51 (0.24–1.11)		0.58 (0.26–1.30)	
	>10	1.15 (0.49–2.67)		1.38 (0.53–3.55)		0.69 (0.37–1.31)		0.84 (0.43–1.65)	

Continued on p. 3058

Table 3—Continued

Drug	Prescription number	Outcome measure: diagnosis of depression				Outcome measure: diagnosis of depression or use of antidepressant			
		HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test	HR (95% CI), partially adjusted	Trend test	HR (95% CI), fully adjusted	Trend test
Liraglutide	1–2	1.00	0.96 (0.85–1.09), $P = 0.530$	1.00	0.95 (0.83–1.08), $P = 0.420$	1.00	1.07 (0.98–1.18), $P = 0.128$	1.00	**1.10 (1.00–1.21), $P = 0.048$**
	0	0.43 (0.30–0.60)		0.59 (0.40–0.86)		0.82 (0.61–1.11)		0.96 (0.71–1.28)	
	3–5	0.75 (0.45–1.25)		0.80 (0.46–1.39)		1.52 (1.02–2.24)		1.48 (1.00–2.19)	
	6–10	1.12 (0.71–1.77)		1.24 (0.75–2.05)		1.59 (1.09–2.30)		1.61 (1.11–2.34)	
	>10	0.82 (0.55–1.23)		0.81 (0.52–1.25)		1.41 (1.02–1.97)		1.49 (1.07–2.08)	
Dapagliflozin	1–2	1.00	0.21 (0.04–1.13), $P = 0.069$	1.00	0.26 (0.05–1.44), $P = 0.123$	1.00	0.75 (0.50–1.14), $P = 0.180$	1.00	0.70 (0.45–1.08), $P = 0.105$
	0	0.67 (0.25–1.78)		0.98 (0.38–2.56)		0.39 (0.24–0.65)		0.43 (0.26–0.71)	
	3–5	0.27 (0.03–2.44)		0.33 (0.04–3.05)		0.69 (0.30–1.60)		0.69 (0.30–1.59)	
	6–10	0.00 (0.00–0.00)		0.00 (0.00–0.00)		0.39 (0.14–1.15)		0.34 (0.10–1.11)	
	>10	0.00 (0.00–0.00)		0.00 (0.00–0.00)		0.91 (0.22–3.83)		0.68 (0.16–3.02)	

Adjustment for age, sex, employment status, and calendar year (partially adjusted) and additional adjustment for somatic diagnoses (fully adjusted). Statistically significant trend tests are highlighted in boldface type.

Further, we added analyses with a combined outcome measure on a diagnosis of depression or the use of antidepressants and thereby systematically confirmed results from the primary analyses. We did not include continued use of antidepressants as a separate outcome measure, as antidepressants are prescribed for conditions other than depression (41). As with all other registers including nationwide medication data, the Danish Register of Medicinal Product Statistics includes no information on adherence or dose of the exposure drugs, although repeat prescriptions are a reasonable proxy of adherence (27). As we estimated the rate of incident depression during successive prescription periods, it is unlikely that nonadherence substantially confounded our results. One final factor may be sequencing; metformin is generally a first-line antidiabetes drug therapy, and pioglitazone is a second-line therapy. As diabetes is a progressive disorder, one might expect people who settle on first-line therapy to have simpler and more benign illness, whereas those needing second-line therapy may have more complex, refractory, or comorbid illness.

Comparisons With Prior Findings

As acknowledged by Moulton et al. (6), the evidence from RCTs of effects of antidiabetes drugs on depression is limited due to several factors including small RCTs of varying quality rarely designed to test effects of antidiabetes drugs on depression, as summarized above. Our findings of decreased risk of developing depression with continued use of metformin partly contrast with the results by Moulton et al. (6), as metformin was nonsignificantly superior to placebo in the meta-analysis including three trials comprising a total of 2,420 patients. There may be several explanations for these discrepancies. First, among the three RCTs included in the meta-analysis of Moulton et al. (6), one unpublished study by Lustman et al. in which metformin performed similarly to placebo appears, and excluding this study from the meta-analysis might result in a statistically significant effect favoring metformin over placebo in reducing depressive symptoms. Among the two remaining studies on metformin versus placebo, only the study by Guo et al. (15) showing a positive effect on depression was specifically designed to investigate the effect of metformin, as it included patients with depression at baseline, whereas the study by Ackermann et al. (20) included patients without depressive symptoms at baseline with a very low score on the Beck Depression Inventory, 4.6 (SD 4.6), and depression as a secondary outcome measure. Nevertheless, as emphasized by Moulton et al. (6), this finding should be considered with caution due to high between-study heterogeneity including patients with poststroke depression (16), polycystic ovarian syndrome (18), Parkinson disease, metabolic syndrome (21), and bipolar depression (22,23) and a lack of large trials, as the number of included patients was <50 in all trials (6), except one including 118 patients with poststroke depression and diabetes (16). Recently, metformin was proven to have antidepressant effects in patients without diabetes with major depression (14).

In relation to pioglitazone, one may, based on our findings, speculate whether weight gain associated with pioglitazone may add to increasing the risk of depression. Danish register data do not include information on body weight.

In accordance with our findings, the GLP-1 receptor agonist liraglutide was, compared with usual care in a single trial including 50 patients, associated with a nonsignificant improvement in depressive symptoms as a secondary outcome (42). Similarly, insulin had no effect on depressive symptoms in a single RCT including 57 patients with poorly controlled type 2 diabetes (43), in accordance with our negative overall findings.

Conclusion

Using real-life population-based data, we were able to confirm previous albeit weak evidence of an antidepressant effect of metformin (and combinations of drugs including metformin). This evidence should be used in guiding prescriptions for patients with type 2 diabetes who are at risk for developing depression including those with prior depression or anxiety and patients with a family history of depression. In relation to pioglitazone, our findings serve to question whether this antidiabetes drug has a positive effect on depression, as suggested by prior smaller studies.

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