BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023830
Article Type:	Research
Date Submitted by the Author:	22-Jun-2018
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Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Depression & mood disorders < PSYCHIATRY, cohort study, pharmacoepidemiology

A Cohort Study Examining the Risk of Depression or Self-Harm Associated with Incretin-based Therapies Used to Manage Hyperglycemia in Patients with Type 2 Diabetes

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Abbreviated Title: Depression and Self-Harm Among Incretin-based Therapy Users

Key terms: cohort study, type 2 diabetes, dipeptidyl-peptidase 4 inhibitors, glucagon-like receptor 1 agonists, depression, suicide, self-harm

Counts: Abstract=294; Manuscript= 3078; Figures=3; Tables=3; References=49

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Abstract

Objectives: To compare population-based incidence rates of new-onset depression or self-harm in patients initiating incretin-based therapies with that of sulfonylureas (SU) and other glucose-lowering agents.

Design: Population-based cohort study

Setting: Patients attending primary care practices registered with the UK-based Clinical Practice Research Datalink (CPRD).

Participants: Using the UK-based Clinical Practice Research Datalink (CPRD), we identified two incretin-based therapies cohorts: (1) DPP-4i-cohort, consisting of new-users of DPP-4 inhibitors and sulfonylureas, and (2) GLP-1RA-cohort, consisting of new-users of GLP-1 receptor agonists and sulfonylureas, between Jan-2007 and Jan-2016. Patients with a prior history of depression, self-harm, and other serious psychiatric conditions were excluded.

Main outcome measures: The primary study outcome comprised a composite of new-onset depression or self-harm. Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Deciles of high-dimensional propensity scores and concurrent number of glucose-lowering agents were used to adjust for potential confounding.

Results: We identified new-users of 6206 DPP-4i and 22128 sulfonylureas in the DPP-4i-cohort, and 501 GLP-1RA and 16409 sulfonylurea new-users in the GLP-1RA-cohort. The incidence of depression or self-harm was 8.2 vs. 11.7 events/1000-person-years (unadjusted hazard ratio (HR): 0.70, 95% confidence internal (CI): 0.51-0.96) in the DPP-4i-cohort and 18.2 vs. 13.6 events/1000-person-years (unadjusted hazard ratio (HR): 1.36, 95% confidence internal (CI): 0.72-2.58) in the GLP-1RA-cohort for incretin-based therapies vs sulfonylureas, respectively. Following adjustment for potential confounding, incretin-based therapies did not have an increased or decreased incidence of depression or self-harm compared to sulfonylureas (adjusted HR [DPP-4i-cohort]: 0.80, 95% CI: 0.57-1.13; adjusted HR [GLP-1RA-cohort]: 1.25, 95% CI: 0.63-2.50). Consistent results were observed for other glucose-lowering comparators including insulin and thiazolidinediones.

Conclusions: Our findings suggest that the two incretin-based therapies are not associated with an increased or decreased risk of depression or self-harm.

Article Summary

- Incretin-based therapies, dipeptidyl peptidase-4 inhibitors [DPP-4i] and glucagon-like peptide-1 receptor agonists [GLP-1RA], used to manage hyperglycemia in patients with type 2 diabetes may have neuropsychiatric effects due to GLP-1 receptor expression in the central nervous system
- This study found that initiation of an incretin-based therapy, either a DPP-4 inhibitor or a GLP-1 receptor agonist, does not appear to substantially increase or decrease the risk of depression or self-harm in patients with type 2 diabetes

Strengths and limitations of the study

- This study used a new-user active comparator design with high dimensional propensity scores to control for confounding
- This study cannot rule out small or modest difference in risk of depression or self-harm between incretin-based therapy users and other glucose-lowering due to study power limitations

Introduction

Patients with diabetes frequently have coexisting depression with a prevalence ranging from 12% to 27%.[1] Depression is not only associated with diabetes but with an increased risk of diabetes-related complications,[2] decreased quality of life,[3] and decreased life-expectancy.[4] Diabetes is also associated with new-onset depression; however, the temporal association between diabetes and depression remains unclear.[5,6] Moreover, diabetes is associated with an increased risk of intentional self-harm,[7,8] albeit there is significant heterogeneity between studies assessing the association between diabetes and suicide.[9] It has been postulated that certain glucose-lowering pharmacotherapies may have a positive influence on the symptoms of depression, although the evidence is sparse.[10–15] The incretin-based therapies in particular may have neuropsychiatric effects given the presence of glucagon-like peptide-1 (GLP-1) receptors in the central nervous system.[20,21]

Concerns surrounding central nervous system effects stem from a case report of exenatide-induced depression and from pooled adverse event data from pre-marketing clinical trials for sitagliptin.[22–24] Pooled event rates for the latter suggested a 4-fold increased risk of suicide ideation and completed suicide in sitagliptin users compared to non-

users.[23,25] Animal models suggest adverse neuropsychiatric effects are biologically plausible given the expression of GLP-1 receptors in the brain.[20] Furthermore, studies have shown low dipeptidyl peptidase-4 (DPP-4) activity is correlated with depression.[26–28] Although the case-report mentioned above suggested a potential increased risk of depression, a recent study reported positive effects of GLP-1 receptor agonists on patients well-being.[29] Therefore alternations in DPP-4 enzymatic activity may modulate the pathophysiology of neuropsychiatric conditions such as major depression.

Using data from a population-based cohort of patients with type 2 diabetes, we aimed to quantify the association between incretin-based therapies and the composite of new-onset depression and self-harm.

Methods

Study Design and Data Sources

We conducted a population-based cohort study using data from the Clinical Practice Research Datalink (CPRD), which captures electronic medical information for primary care encounters by general practitioners in the United Kingdom (UK).[30] The CPRD contains de-identified individual-level longitudinal data collected from a subset of primary care practices (~700) in the UK. The CPRD data is a representative sample that is similar to the overall UK population in age, sex, and ethnicity.[31] The database includes sociodemographic and lifestyle variables (e.g., alcohol consumption), physiological measures (e.g., blood pressure), laboratory testing (e.g., glycated hemoglobin [A1c]), physician-assigned diagnoses using the Read classification system, and prescription records from general practitioner records. Data quality checks are performed in accordance with standardized guidelines that certify practices as up-to-standard. Furthermore, over 350 validation studies have been performed using the CPRD.[32,33] Information on hospitalizations and causes of death are available for a subset of CPRD patients through linkages with the external databases. Details regarding the data quality, linkages, and utility are available elsewhere.[34] The CPRD has been used extensively to study associations between drugs and depression and self-harm.[35–39] Our study protocol was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA, August 2017) and received approval from the Health Research Ethics Board at Memorial University.

Study Cohorts

Our source population consisted of all patients over 18 years of age with a minimum of 12-months of up-to-standard medical history in the CPRD database that received a new diagnosis for type 2 diabetes or a new prescription for any glucose-lowering therapy between January 1, 2001 and the February 2016 CPRD dataset build. We used a 365-day washout period to define a new diagnosis or new glucose-lowering therapy use. A sub-cohort of patients (~58%) selected from the source population was linked to Hospital Episode Statistics (HES – follow-up until 31March2014), Office of National Statistics (ONS – follow-up until 30April2014), and index of multiple deprivation (IMD [2010]) data to capture hospital records, causes of death, and socioeconomic status information, respectively. Women with polycystic ovarian syndrome, gestational diabetes, or whom were pregnant during the study period were

excluded. In addition, we excluded patients with a study entry date prior to January 1, 2007 as the first incretin-based therapies became available in the UK in early 2007.

We identified two main study cohorts. Specifically, the first cohort consisted of new-users of DPP-4 inhibitors and new-users of sulfonylureas (DPP-4 inhibitor cohort) and the second cohort consisted of new-users of GLP-1 receptor agonists and new-users of sulfonylureas (GLP-1 receptor agonist cohort). Although new-users of sulfonylureas served as the reference population for both cohorts, these individuals were selected separately for cohort as prior use of other non-incretin glucose-lowering agents was permitted. To minimize potential selection bias within the above cohorts, we excluded patients with a history of depression, self-harm, anxiety, and other serious psychiatric conditions in the year prior to a patient's cohort entry date.

Exposure and Outcome Definitions

Within each incretin-based therapy cohort, we defined person-time exposure to all classes of glucose-lowering therapy including (1) DPP-4 inhibitors, (2) GLP-1 receptor agonists, (3) Sulfonylureas, (4) Metformin, (5) Thiazolidinediones, (6) Sodium glucose co-transporter-2 inhibitors, (7) Meglitinides, (8) Acarbose, (9) Insulin, and (10) no glucose-lowering drug therapy (i.e. diet/lifestyle). Patient's contributed person-time to each of the aforementioned categories on the day of their first prescription or date of diagnosis (defined as the patient's index date) until a patient discontinued the drug, left a CPRD practice, died, or on the final date of follow-up, whichever occurred first. To account for potential non-adherence, we included a portion of follow-up time following the end of the expected medication supply that was equivalent to 50% of the prescription duration as a period of exposure.

Our primary outcome the composite of either new-onset depression or self-harm, including suicide and suicidal ideation. If a patient experienced more than one event, the date of the first event was used. New-onset depression or episodes of self-harm were identified using diagnostic codes from either the CPRD, HES, or ONS data sources (specific codes available in supplemental material in Appendices A and B).

Statistical Analysis

Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Our primary exposure contrasts of interest were DPP-4 inhibitors vs. sulfonylureas and GLP-1 receptor agonists vs. sulfonylureas within the DPP-4 inhibitor and GLP-1 receptor agonists cohorts respectively. Sulfonylureas were chosen a priori as the main reference group given their use in clinical practice as second or third agents resembles incretin-based therapies. Patients contributed follow-up time from the initiation of the incretin-based therapy of interest or comparator until they experienced the composite outcome of interest or were censored. Censoring occurred upon the earliest date of the following events: discontinuation of the incretin-based therapy of interest or comparator, switching between an incretin-based therapy to the comparator (or vice-versa), leaving a CPRD practice site, death, end of study period.

To adjust for potential confounders, we used a high-dimensional propensity score (hdPS) algorithm to select up to 40 empirical covariates.[40] Using a multivariable logistic regression model that included the both empirically derived and predefined (age, sex, alcohol abuse, body mass index, duration of treated diabetes, comorbidities, number of hospitalizations, HbA1c, prior medications use, smoking status, socioeconomic status [quintiles of the index of multiple deprivation], use of other glucose-lowering therapies, year of cohort entry. A detailed list of covariates forced into propensity score model is shown in Appendix C) covariates, we calculated the probability of initiating a DPP-4 inhibitor versus a sulfonylurea (or comparator for sensitivity analysis). Patients with overlapping propensity scores were included in the analysis. A separate hdPS procedure was run for the GLP-1 receptor agonist cohort. Adjusted hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards regression model with deciles of the hdPS and variable indicating the number of glucose-lowering agents during follow-up (1, 2, 3 or more). We used standard graphical approaches to assess model assumptions for which no violations were noted.

Secondary analyses included alternative comparator groups and components of composite outcome (i.e., depression and self-harm as separate outcomes). In addition, we conducted several additional sensitivity analyses. First, we used two alternative methods to adjust for potential confounding including a matched propensity score approach (1:1 -

matching using greedy nearest neighbor approach with a caliper set at 0.2 times the standard deviation of the natural logarithm of the propensity score) and grouping patients with identical patterns of glucose-lowering therapies prior to and following cohort initiation. For the latter approach, an example of how we grouped patients is as follows. Patients who started with metformin monotherapy and added an incretin-based therapy would be grouped with patients who also started metformin monotherapy and then added the comparator drug of interest. Groups with less than 25 patients were excluded from this analysis. We used a categorical variable to adjust for all groups within our multivariable Cox proportional hazards model. Second, we ran several analyses using restricted cohorts including restricting our cohort to patients eligible for HES/ONS linkage (i.e., patients with hospital and death certificate records), restricting to monotherapy users, restricting to a cohort of metformin monotherapy users who added the incretin-based therapy of interest or a sulfonylurea. Third, we added BMI (as a categorical variable) to Cox proportional hazards model given that weight may be a confounding factor.[41,42] Fourth, we used time-dependent variables to classify our exposures of interest throughout follow-up time. All analyses were conducted with R version 3.3.3.

Results

DPP-4 Inhibitor Cohort

Within the DPP-4 inhibitor new user cohort, there were 6206 initiators of a DPP-4 inhibitor and 22128 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 324 (362) days for DPP-4 inhibitor users and 299 (385) days for sulfonylurea users. Compared to sulfonylurea users, DPP-4 inhibitor users were on average younger, had fewer hospitalizations in the year prior to cohort entry, and less likely to have impaired kidney function. Patient characteristics were well-balanced following propensity score matching (Table 1). There were a total 264 patients identified with new-onset depression or self-harm.

The incidence of depression or self-harm was 8.2 per 1000 person-years in DPP-4 inhibitor users compared to 11.7 per 1000 person-years in sulfonylurea users (unadjusted hazard ratio (HR): 0.70 95% confidence interval (CI) 0.51-0.96 [table 3]). Similarly, the crude incidence rates were smaller for DPP-4 inhibitor users versus other comparators (10.0 vs. 10.8 per 1000 person-years for TZDs; 9.8 vs. 20.7 for insulin users). However, following

adjustment for potential confounding variables, there was no significant association between DPP-4 inhibitor use and the risk of depression or self-harm for all comparator groups (sulfonylurea comparator: adjusted HR 0.80, 95% CI 0.57-1.13; TZD comparator: adjusted HR 1.17, 95% CI 0.70-1.96; insulin comparator: adjusted HR 0.98, 95% CI 0.53-1.83). Appendices D and E show the results for the risks of depression and self-harm separately.

GLP-1 Receptor Agonist Cohort

Within the GLP-1 receptor agonist cohort, there were 501 initiators of a GLP-1 receptor agonist and 16409 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 397 (409) days for GLP-1 receptor agonist users and 292 (373) days for sulfonylurea users. Compared to sulfonylurea users, GLP-1 receptor agonist users were on average younger, more likely female, used more drugs in the year prior to cohort entry, had a lower baseline HbA1c, more likely to have used several medications prior to cohort entry including insulin, SSRIs, or other antidepressant. Following propensity score matching, baseline patient characteristics were well-balanced (Table 2). There were a total 193 patients identified with new-onset depression or self-harm.

The incidence rate of depression or self-harm was non-significantly higher for GLP-1 receptor users compared to sulfonylurea users (18.2 vs. 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72-2.58; adjusted HR 1.25, 95% CI 0.63-2.50), TZDs (16.4 vs. 12.5 per 1000 person-years; unadjusted HR 1.32, 95% CI 0.72-2.42; adjusted HR 1.18. 95% CI 0.53-2.65), and insulin users (13.6 vs. 20.7 per 1000 person-years; unadjusted HR 0.74, 95% CI 0.35-1.56; adjusted HR 1.07, 95% CI 0.39-2.94). All measured associations remained non-significant following adjustment for potential confounders (Table 3). Appendix D shows the results for depression analyzed as a separate outcome. We were unable to analyze results for self-harm separately, due to small numbers of events (Appendix E).

Sensitivity Analyses

Figures 2 and 3 provide the number of events per treatment exposure group and measures of association for selected sensitivity analyses across the main DPP-4 inhibitor and GLP-1 receptor agonist cohorts. There were too few events to run a stable statistical model for all pre-specified sensitivity analyses (e.g. new monotherapy users); however, findings from

models that were run were consistent with our main results suggesting that DPP-4 inhibitor use did not have an increased or decreased risk of new-onset depression (Appendix G to L).

Patient and Public Involvement

No patients were involved in any aspect of the study.

Discussion

New users of DPP-4 inhibitors and new users of GLP-1 receptor agonists did not have an increased or decreased risk of a new diagnosis of depression or episode of self-harm. These findings extend our current knowledge regarding the relative safety of the incretin-based therapies used to manage hyperglycemia in patients with type 2 diabetes.

The impetus for our study was the safety signal generated by randomized controlled trials and a case-report suggesting that incretin-based therapies may affect the risk of depression or self-harm. Specifically, early trial data found a 4-times greater risk of suicidal ideation or completed suicide in sitagliptin users vs glipizide users.[23,25] A higher incidence of depression was also observed in the long-term safety population among phase-3 clinical trial in sitagliptin 100mg users (13/429) compared to placebo (0/154); however, the incidence of psychiatric events was no different among pooled phase 3 studies (3.0% in sitagliptin 100mg users; 2.4% in sitagliptin 200mg users, and 3.2% in placebo users).[24] Moreover, a case-report has also been published regarding exenatide-induced depression.[22]

Despite our findings suggesting a lack of association between incretin-based agents and depression or self-harm, there is a substantial evidence-base from animal models that suggest incretin-based therapies may affect mood disorders. Anderberg and colleagues found differential effects of acute versus chronic exposure to a GLP-1 receptor agonist.[43] Acute activation of GLP-1 receptors was associated with anxiogenic effects, whereas chronic GLP-1 receptor activation did not elicit anxiogenic effects in Sprague-Dawley rats. In fact, chronic exposure to a GLP-1 receptor agonist was associated with a decrease in depressive-like behavior. Furthermore, acute stimulation of GLP-1 receptors affected serotonin turnover and serotonin receptor expression in the amygdala; however, chronic stimulation did not affect serotonin turnover or receptor expression. In addition to effects on serotonin, activation of GLP-1 may have mood effects through impacting central dopamine levels.[44] A mice model

suggests that liraglutide, a GLP-1 receptor agonist, has antipsychotic properties possibly through its affecting dopamine activity in the brain.[45] Interestingly, the DPP-4 inhibitor sitagliptin, did not exhibit the same antipsychotic properties.

Another possible mechanism by which glucose lowering therapies may affect mood disorders is through the reduction in inflammatory cytokines/mediators. Moulton et al reported improvement in depressive symptoms over 1-year in a cohort of 1735 newly diagnosed patients with type 2 diabetes.[10] The improvement in depressive symptoms measure by the PHQ-9 was independent of change in glycemic control and was correlated with a change in the inflammatory marker hs-CRP. Furthermore, a meta-analysis found that pioglitazone was associated with a reduction in symptoms of depression compared to placebo (pooled odds ratio = 3.3, 95% confidence interval 1.4 to 7.8).[11] A 12-week open-label study also found that pioglitazone was associated with a reduction in depression symptoms as well as a decrease in c-reactive protein and decreased insulin resistance.[12] Indeed, a population-based cross-sectional study found that numerous inflammatory markers (e.g., c-reactive protein, inerleukin-1 receptor agonist, monocyte chemotactic protein-1, white blood cell count, triglyceride) were associated with depression in patients with type 2 diabetes.[46] To further test this hypothesis among DPP-4 inhibitor users, there is an ongoing small clinical trial evaluating the effect of sitagliptin on symptoms of depression in the elderly (EudraCT Number: 2015-004527-32).[47]

Our study is subject to the standard limitations of observational cohort studies including the potential for residual and unmeasured confounding. Although we adjusted for over 70 potential confounders using an HdPS approach, we were not able to capture all relevant potential confounders such as severity of depressive symptoms and patient level socioeconomic status. Our follow-up time was also limited (DPP-4 cohort mean follow-up time = 305 days; GLP-1 receptor agonist cohort mean follow-up = 296 days), therefore, it is possible that a longer time frame was required to detect an association. However, it would be expected that an effect on depression symptoms mediated by serotonin or dopaminergic central pathways would be apparent after 4 to 6 weeks or sooner. There were a limited number of self-harm events and our study was not powered to detect clinically relevant differences across exposure groups for this component of our composite outcome. Similarly, given the lower and upper limits of the 95% confidence intervals, our study cannot rule out small or moderate differences in the risk of depression across exposure groups.

Misclassification of the exposure or outcome variables of interest may have also impacted our findings. Our exposure variables of interest (incretin-based therapies) were measured based on primary care prescription records and therefore may overestimate true exposure due to primary and secondary non-adherence. In addition, prescriptions written by specialists are not captured in the CPRD. It is possible that when the incretin-based therapies were introduced they were more frequently prescribed by specialists and our study would miss the initial prescription, however, subsequent prescriptions written by general practitioners would be captured. Previous studies have shown that depression is likely underestimated using diagnostic codes, although positive predictive values have generally been greater than 90% using ICD-10 codes.[48] Under-ascertainment of depression would likely be non-differential between our exposure groups of interest and therefore bias our findings toward the null. Suicide and self-harm have also been shown to be underestimated using CPRD data and the use of linked mortality data via the Office of National Statistics improves the sensitivity for capturing suicide and self-harm; however, underreporting of events is still expected.[49] In addition, the role of incretin-based agents may have shifted over time whereby when they were first introduced to the market were not used commonly as 2nd line agents and sulfonylureas may have been used as first or second-line agents. We attempted to control for both temporal trends and timing of therapy by using calendar time, duration of and prior exposure of glucose-lowering therapies as covariates in the propensity score.

Our findings provide some reassurance regarding the safety of the incretin-based therapies in the treatment of type 2 diabetes. Specifically, our study results suggest that there is not a clinically relevant association between either DPP-4 inhibitors or GLP-1 receptor agonists and depression or self-harm.

Authors' Contributions: JMG, EC, WKM, LKT and SRM, were involved in the concept and design of the study. JMG was responsible for drafting the first version of the manuscript. All authors contributed to the interpretation of data. JMG, EC, WKM, and LKT provided revisions to the manuscript. JMG will act as guarantor for the study.

Acknowledgements: JMG is supported as a New Investigator Award from the Canadian Institute of Health Research and a Clinician Scientist Award from Diabetes Canada. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the author/s alone.

Funding Support: This work was supported by an operating grant from the Canadian Institute for Health Research (FRN173599 – 287647).

Competing Interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships that may be relevant to the submitted work; and no other relationships or activities that could appear to have influence the submitted work.

Ethical approval: This study was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA) and received approval from the Health Research Ethics Board at Memorial University.

located; and, vi) licence any third party to do any or all of the above.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing: no additional data available.

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TABLES

Table 1. Patient Characteristics of New-user DPP-4 Inhibitor Cohort Before and After Propensity Score Matching. and GLP-1 Receptor Agonist Cohorts.

	DPP4 Inhibitor New User Cohort Before Propensity Score Matching		DPP4 Inhibitor New User Cohort After Propensity Score Matching	
	DPP-4i (n=6206)	SU (n=22128)	DPP-4i (n=6008)	SU (n=6008)
Age in yrs (sd)	58(12.2)	60.5(13.8)	58.1(12.2)	58.2(12.5)
Female	2258(36.4%)	8107(36.6%)	2189(36.4%)	2187(36.4%)
Measure of deprivation				
Least	624(10.1%)	2492(11.3%)	603(10%)	594(9.9%)
Most	615(9.9%)	2342(10.6%)	603(10%)	614(10.2%)
Unknown	2862(46.1%)	8780(39.7%)	2739(45.6%)	2683(44.7%)
Diabetes duration in yrs (sd)	2.0(1.8)	1.0(1.5)	1.9(1.7)	1.9(1.8)
Body Mass Index >30	4162(67.1%)	10661(48.2%)	3994(66.5%)	3978(66.2%)
Number of hospitalizations in year prior to cohort entry				
0	5647(91%)	18516(83.7%)	5452(90.7%)	5470(91%)
1	378(6.1%)	2105(9.5%)	375(6.2%)	379(6.3%)
2	109(1.8%)	784(3.5%)	109(1.8%)	92(1.5%)
3+	72(1.2%)	723(3.3%)	72(1.2%)	67(1.1%)
Number of drugs in year prior to cohort entry				
0-4	721(11.6%)	3098(14%)	703(11.7%)	671(11.2%)
5-10	3204(51.6%)	10379(46.9%)	3081(51.3%)	3119(51.9%)
11+	2281(36.8%)	8651(39.1%)	2224(37%)	2218(36.9%)
HbA1c				
<6.5%	242(3.9%)	1393(6.3%)	238(4%)	233(3.9%)
6.5-7.5%	1104(17.8%)	3349(15.1%)	1049(17.5%)	1053(17.5%)
7.5-9%	2831(45.6%)	7121(32.2%)	2701(45%)	2694(44.8%)
9%+	2000(32.2%)	9833(44.4%)	1991(33.1%)	2007(33.4%)
Unknown	29(<1%)	432(2%)	29(<1%)	21(<1%)
e*GFR* <60	883(14.2%)	4429(20%)	857(14.3%)	890(14.8%)
Diagnoses in year prior to cohort entry				
Heart Failure	68(1.1%)	369(1.7%)	68(1.1%)	51(<1%)
Hypertension	1095(17.6%)	4475(20.2%)	1066(17.7%)	1087(18.1%)
Dyslipidemia	213(3.4%)	1093(4.9%)	213(3.5%)	212(3.5%)
Ischemic heart	174(2.8%)	1033(4.7%)	171(2.8%)	168(2.8%)
Peripheral vascular	25(<1%)	145(<1%)	25(<1%)	24(<1%)
Prescription drug use in year prior to cohort entry				
Metformin	5775(93.1%)	16534(74.7%)	5578(92.8%)	5638(93.8%)
Acarbose	S	8(<1%)	S	S
SGLT2 inhibitors	38(<1%)	93(<1%)	38(<1%)	40(<1%)
Meglitinide	47(<1%)	39(<1%)	38(<1%)	29(<1%)
Thiazolidinedione	252(4.1%)	403(1.8%)	222(3.7%)	209(3.5%)
Insulin	82(1.3%)	331(1.5%)	80(1.3%)	86(1.4%)
Hypnotic	332(5.3%)	1486(6.7%)	328(5.5%)	324(5.4%)
Mood	85(1.4%)	280(1.3%)	81(1.3%)	83(1.4%)
Anticonvulsant	271(4.4%)	832(3.8%)	260(4.3%)	266(4.4%)
Antipsychotics	176(2.8%)	829(3.7%)	172(2.9%)	171(2.8%)

S = suppressed due to low number of events

Table 2. Patient Characteristics of New-user GLP-1 Receptor Agonist Cohort Before and After Propensity Score Matching.

	GLP-1 Receptor Agonist New User Cohort Before Propensity Score Matching		GLP-1 Receptor Agonist New User Cohort After Propensity Score Matching	
	GLP-1RA (n=501)	**SU (n=16409)**	**GLP-1RA (n=488)**	**SU (n=488)**
Age in yrs (sd)	49.4(11.3)	57.8(12.9)	49.7(11.2)	49.2(12.6)
Female	204(40.7%)	6021(36.7%)	198(40.6%)	174(35.7%)
Measure of				
Least	40(8%)	1688(10.3%)	40(8.2%)	29(5.9%)
Most	56(11.2%)	1770(10.8%)	56(11.5%)	52(10.7%)
Unknown	240(47.9%)	6784(41.3%)	230(47.1%)	214(43.9%)
Diabetes duration in yrs (sd)	1.7(1.6)	1.2(1.6)	1.7(1.6)	1.7(1.8)
Body Mass Index>30	470(93.8%)	10481(63.9%)	458(93.9%)	452(92.6%)
Number of hospitalizations in year prior to cohort entry				
0	456(91%)	14170(86.4%)	445(91.2%)	437(89.5%)
1	29(5.8%)	1344(8.2%)	28(5.7%)	27(5.5%)
2	10(2%)	499(3%)	9(1.8%)	17(3.5%)
3+	6(1.2%)	396(2.4%)	6(1.2%)	7(1.4%)
Number of drugs in year prior to cohort entry				
0-4	17(3.4%)	1660(10.1%)	17(3.5%)	18(3.7%)
5-10	195(38.9%)	7899(48.1%)	192(39.3%)	208(42.6%)
11+	289(57.7%)	6850(41.7%)	279(57.2%)	262(53.7%)
HbA1c				
<6.5%	66(13.2%)	1085(6.6%)	62(12.7%)	66(13.5%)
6.5-7.5%	99(19.8%)	2593(15.8%)	97(19.9%)	99(20.3%)
7.5-9%	150(29.9%)	5357(32.6%)	145(29.7%)	134(27.5%)
9%+	179(35.7%)	7068(43.1%)	177(36.3%)	178(36.5%)
Unknown	7(1.4%)	306(1.9%)	7(1.4%)	11(2.3%)
e*GFR* <60	36(7.2%)	2821(17.2%)	35(7.2%)	40(8.2%)
Diagnoses in year prior to cohort entry				
Heart Failure	5(1%)	244(1.5%)	5(1%)	6(1.2%)
Hypertension	107(21.4%)	3398(20.7%)	106(21.7%)	104(21.3%)
Dyslipidemia	16(3.2%)	771(4.7%)	16(3.3%)	23(4.7%)
Ischemic heart	11(2.2%)	644(3.9%)	11(2.3%)	9(1.8%)
Peripheral	S	106(<1%)	S	S
Prescription drug use in year prior to cohort entry				
Metformin	457(91.2%)	13542(82.5%)	445(91.2%)	449(92%)
Acarbose	2(<1%)	7(<1%)	1(<1%)	1(<1%)
SGLT2 inhibitors	5(1%)	87(<1%)	5(1%)	5(1%)
Meglitinide	11(2.2%)	39(<1%)	10(2%)	10(2%)
Thiazolidinedione	38(7.6%)	376(2.3%)	38(7.8%)	41(8.4%)
Insulin	65(13%)	307(1.9%)	55(11.3%)	59(12.1%)
Hypnotic	32(6.4%)	1093(6.7%)	32(6.6%)	35(7.2%)
Mood	10(2%)	228(1.4%)	10(2%)	8(1.6%)
Anticonvulsant	33(6.6%)	682(4.2%)	31(6.4%)	32(6.6%)
Antipsychotics	12(2.4%)	507(3.1%)	**12(2.5%)**	12(2.5%)

S = suppressed due to low number of events

Table 3. Measures of frequency and association for depression or self-harm in new-users of DPP-4 Inhibitors (DPP4i) or new-users of GLP-1 receptor agonists (GLP1ra) vs. sulfonylureas (SU), thiazolidinediones (TZD), or insulin.

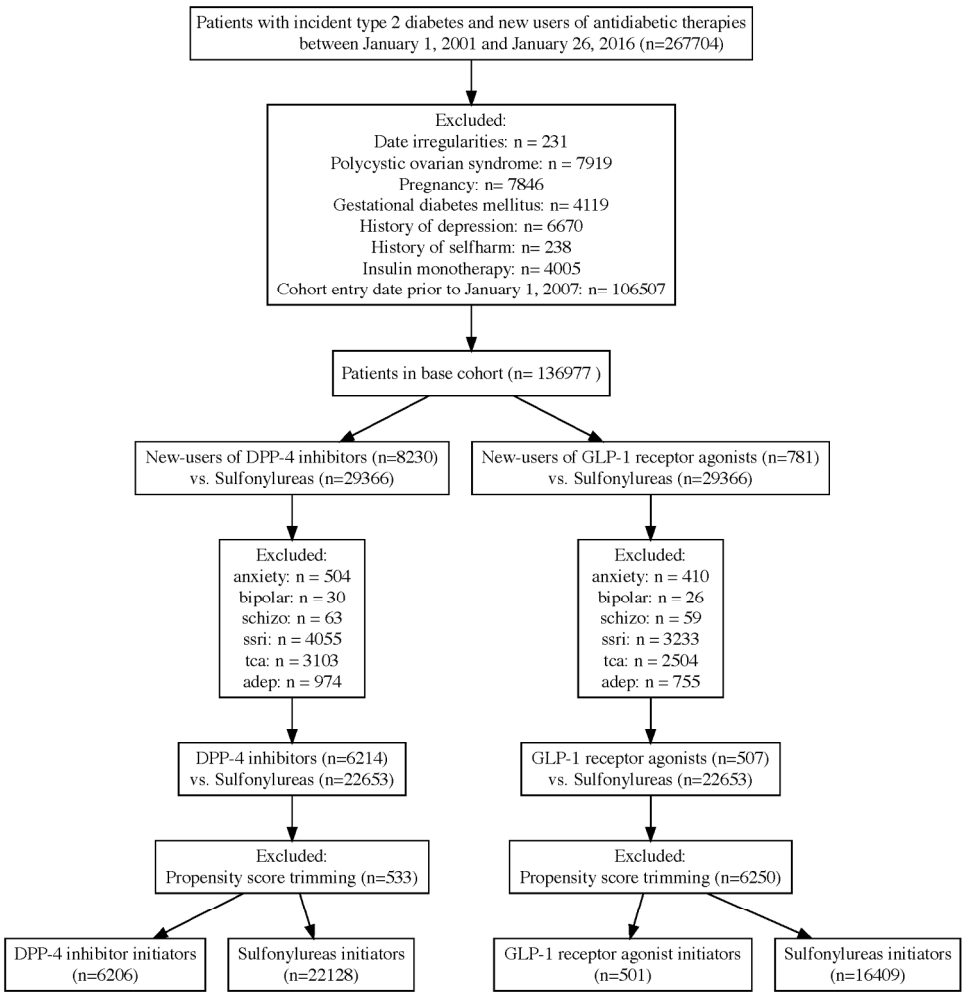
	DPP4 Inhibitor New User Cohort		GLP1 Receptor Agonist New User Cohort	
COMPARATOR: SU				
	DPP4i	**SU**	**GLP1ra**	**SU**
Number of patients	6206	22128	501	16409
Person-years of follow-up	5589	18596	549	13418
Number of Events	46	218	10	183
Incidence per 1000 person-years (95%CI)	8.2(6.2-11)	11.7(10.3-13.4)	18.2(10-33.5)	13.6(11.8-15.8)
Crude HR	0.70(0.51-0.96)	-ref-	1.36(0.72-2.58)	-ref-
Adjusted HR	0.80(0.57-1.13)	-ref-	1.25(0.63-2.50)	-ref-
COMPARATOR: TZD				
	DPP4i	**TZD**	**GLP1ra**	**TZD**
Number of patients	9565	2512	851	2011
Person-years of follow-up	9190	2786	1035	2165
Number of Events	92	30	17	27
Incidence per 1000 person-years (95%CI)	10.0(8.2-12.3)	10.8(7.6-15.4)	16.4(10.3-26.3)	12.5(8.6-18.1)
Crude HR	0.90(0.59-1.36)	-ref-	1.32(0.72-2.42)	-ref-
Adjusted HR	1.17(0.70-1.96)	-ref-	1.18(0.53-2.65)	-ref-
COMPARATOR: INSULIN				
	DPP4i	**Insulin**	**GLP1ra**	**Insulin**
Number of patients	10049	3600	854	2745
Person-years of follow-up	9878	1161	1033	919
Number of Events	97	24	14	19
Incidence per 1000 person-years (95%CI)	9.8(8.1-12)	20.7(13.9-30.8)	13.6(8.1-22.7)	20.7(13.3-32.3)
Crude HR	0.54(0.34-0.87)	-ref-	0.74(0.35-1.56)	-ref-
Adjusted HR	0.98(0.53-1.83)	-ref-	1.07(0.39-2.94)	-ref-

FIGURES

Figure 1. Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

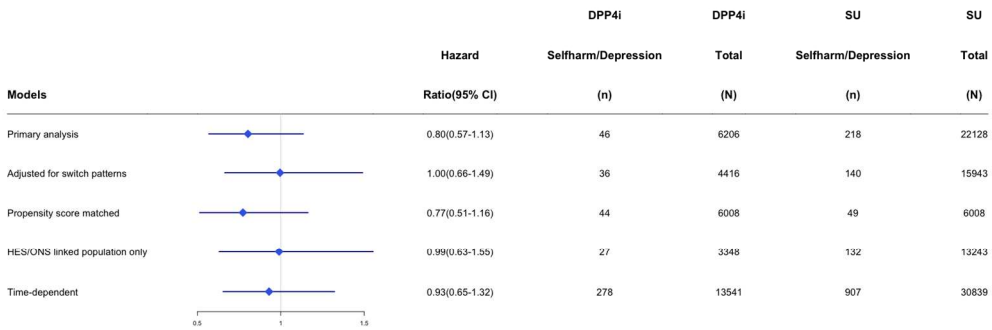
Figure 2. Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Figure 3. Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

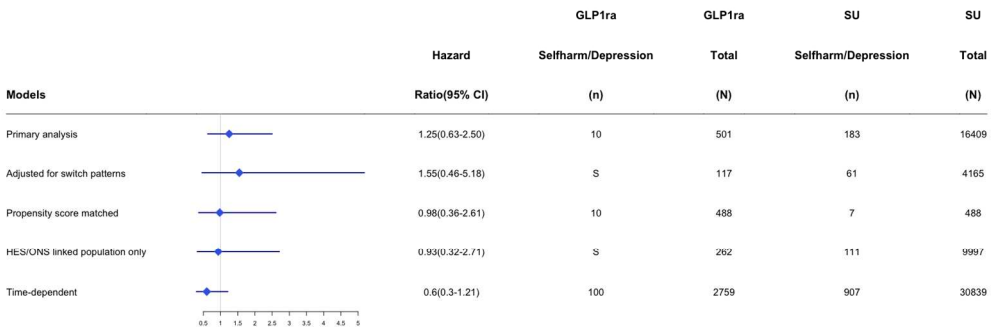


Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

177x181mm (300 x 300 DPI)



Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis



Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Supplementary Material

Appendix A: READ and ICD-10 Codes Used to Identify Depression

READ Code	Description
3004a	Depression
E2b..00	Depressive Disorder Nec
E204.00	Neurotic Depression Reactive Type
1b17.00	Depressed
Eu32z11	[X]Depression Nos
3004am	Mood Depressed
3004er	Reactive Depression
1b17.11	C/O - Feeling Depressed
3004l	Looking Depressed
E112.14	Endogenous Depression
E112.11	Agitated Depression
2960ad	Depression Agitated
E204.11	Postnatal Depression
E135.00	Agitated Depression
ICD-10 Code	Definition
F20.4	post-schizophrenic depression
F31.3	Bipolar affective disorder, current episode mild or moderate depression
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F32.0	Mild depressive episode
F32.1	Moderate depressive episode
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
F32.4	Depressive disorder, single episode in partial remission
F32.5	Depressive disorder, single episode in full remission
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified
F33.0	Recurrent depressive disorder, current episode

	mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified
F34.1	Dysthymia
F34.8	Other persistent mood [affective] disorders
F34.9	Persistent mood [affective] disorder, unspecified
F38.0	Other single mood [affective] disorders
F38.1	Other recurrent mood [affective] disorders
F38.8	Other specified mood [affective] disorders
F39	Unspecified mood [affective] disorder
F41.2	Mixed anxiety and depressive disorder
F99	Mental disorder, not elsewhere specified

Appendix B: READ and ICD-10 Codes Used to Identify Self-harm

READ Code	Description
SL..14	Overdose of biological substance
SL..15	Overdose of drug
SLHz.00	Drug and medicament poisoning not otherwise specified
TK..00	Suicide and self-inflicted injury
TK..11	Cause of overdose â€“ deliberate
TK..12	Injury â€“ self-inflicted
TK..13	Poisoning â€“ self-inflicted
TK..14	Suicide and self-harm
TK..15	Attempted suicide
TK..17	Para-suicide
TK0.00	Suicide + self-inflicted poisoning by solid/liquid substances
TK00.00	Suicide + self-inflicted poisoning by analgesic/antipyretic
TK01.00	Suicide + self-inflicted poisoning by barbiturates
TK01000	Suicide and self-inflicted injury by amylobarbitone
TK01100	Suicide and self-inflicted injury by barbitone
TK01400	Suicide and self-inflicted injury by phenobarbitone
TK02.00	Suicide + self-inflicted poisoning by other sedatives/hypnotics
TK03.00	Suicide + self-inflicted poisoning tranquillizer/psychotropic
TK04.00	Suicide + self-inflicted poisoning by other drugs/medicines

TK05.00	Suicide + self-inflicted poisoning by drug or medicine not otherwise specified
TK06.00	Suicide + self-inflicted poisoning by agricultural chemical
TK07.00	Suicide + self-inflicted poisoning by corrosive/caustic substance
TK0z.00	Suicide + self-inflicted poisoning by solid/liquid substance not otherwise specified
TK1.00	Suicide + self-inflicted poisoning by gases in domestic use
TK10.00	Suicide + self-inflicted poisoning by gas via pipeline
TK11.00	Suicide + self-inflicted poisoning by liquified petrol gas
TK1y.00	Suicide and self-inflicted poisoning by other utility gas
TK1z.00	Suicide + self-inflicted poisoning by domestic gases not otherwise specified
TK2.00	Suicide + self-inflicted poisoning by other gases and vapours
TK20.00	Suicide + self-inflicted poisoning by motor vehicle exhaust gas
TK21.00	Suicide and self-inflicted poisoning by other carbon monoxide
TK2z.00	Suicide + self-inflicted poisoning by gases and vapours not otherwise specified
TK3.00	Suicide + self-inflicted injury by hang/strangulate/suffocate
TK30.00	Suicide and self-inflicted injury by hanging
TK31.00	Suicide + self-inflicted injury by suffocation by plastic bag
TK3y.00	Suicide + self-inflicted injury by other means than hang/strangle/suffocate
TK3z.00	Suicide + self-inflicted injury by hang/strangle/suffocate not otherwise specified
TK4.00	Suicide and self-inflicted injury by drowning
TK5.00	Suicide and self-inflicted injury by firearms and explosives
TK51.00	Suicide and self-inflicted injury by shotgun
TK52.00	Suicide and self-inflicted injury by hunting rifle
TK54.00	Suicide and self-inflicted injury by other firearm
TK5z.00	Suicide and self-inflicted injury by firearms/explosives not otherwise specified
TK6.00	Suicide and self-inflicted injury by cutting and stabbing
TK60.00	Suicide and self-inflicted injury by cutting
TK60100	Self-inflicted lacerations to wrist
TK60111	Slashed wrists self-inflicted
TK61.00	Suicide and self-inflicted injury by stabbing
TK6z.00	Suicide and self-inflicted injury by cutting and stabbing not otherwise specified
TK7.00	Suicide and self-inflicted injury by jumping from high place
TK70.00	Suicide + self-inflicted injury â€“ jump from residential premises
TK71.00	Suicide + self-inflicted injury â€“ jump from other manmade structure
TK72.00	Suicide + self-inflicted injury â€“ jump from natural sites
TK7z.00	Suicide + self-inflicted injury â€“ jump from high place not otherwise specified
TKx.00	Suicide and self-inflicted injury by other means
TKx0.00	Suicide + self-inflicted injury â€“ jump/lie before moving object
TKx0000	Suicide + self-inflicted injury â€“ jumping before moving object
TKx1.00	Suicide and self-inflicted injury by burns or fire
TKx2.00	Suicide and self-inflicted injury by scald
TKx3.00	Suicide and self-inflicted injury by extremes of cold

TKx4.00	Suicide and self-inflicted injury by electrocution
TKx5.00	Suicide and self-inflicted injury by crashing motor vehicle
TKx6.00	Suicide and self-inflicted injury by crashing of aircraft
TKx7.00	Suicide and self-inflicted injury caustic substance
TKxy.00	Suicide and self-inflicted injury by other specified means
TKxz.00	Suicide and self-inflicted injury by other means not otherwise specified
TKy.00	Late effects of self-inflicted injury
TKz.00	Suicide and self-inflicted injury not otherwise specified
U2..00	[X]Intentional self-harm
U2..11	[X]Self-inflicted injury
U2..12	[X]Injury â€“ self-inflicted
U2..13	[X]Suicide
U2..14	[X]Attempted suicide
U2..15	[X]Para-suicide
U20.00	[X]Intentional self-poisoning/exposure to noxious substances
U20.11	[X]Deliberate drug overdose/other poisoning
U200.00	[X]Intentional self-poisoning/exposure to non-opioid analgesic
U200.11	[X]Overdose â€“ paracetamol
U200.12	[X]Overdose â€“ ibuprofen
U200.13	[X]Overdose â€“ aspirin
U200000	[X]Intentional self-poisoning/exposure to non-opioid analgesic at home
U200100	[X]Intentional self-poisoning non-opioid analgesic at residential institution
U200400	[X]Intentional self-poisoning non-opioid analgesic in street/highway
U200500	[X]Intentional self-poisoning non-opioid analgesic trade/service area
U200y00	[X]Intentional self-poisoning non-opioid analgesic other specified place
U200z00	[X]Intentional self-poisoning non-opioid analgesic unspecifified place
U201.00	[X]Intentional self-poisoning/exposure to antiepileptic
U201000	[X]Intentional self-poisoning/exposure to antiepileptic at home
U201z00	[X]Intentional self-poisoning antiepileptic unspecified place
U202.00	[X]Intentional self-poisoning/exposure to sedative hypnotic
U202.11	[X]Overdose â€“ sleeping tablets
U202.12	[X]Overdose â€“ diazepam
U202.13	[X]Overdose â€“ temazepam
U202.15	[X]Overdose â€“ nitrazepam
U202.16	[X]Overdose â€“ benzodiazepine
U202.17	[X]Overdose â€“ barbiturate
U202.18	[X]Overdose â€“ amobarbital
U202000	[X]Intentional self-poisoning /exposure to sedative hypnotic at home
U202400	[X]Intentional self-poisoning sedative hypnotic in street/highway
U202y00	[X]Intentional self-poisoning sedative hypnotic other specified place
U202z00	[X]Intentional self-poisoning sedative hypnotic unspecified place
U204.00	[X]Intentional self-poisoning/exposure to psychotropic drug
U204.11	[X]Overdose â€“ antidepressant

U204.12	[X]Overdose â€“ amitriptyline
U204.13	[X]Overdose â€“ SSRI
U204000	[X]Intentional self-poisoning /exposure to psychotropic drug at home
U204100	[X]Intentional self-poisoning psychotropic drug at residential institution
U204y00	[X]Intentional self-poisoning psychotropic drug other specified place
U204z00	[X]Intentional self-poisoning psychotropic drug unspecified place
U205000	[X]Intentional self-poisoning/exposure to narcotic drug at home
U205y00	[X]Intentional self-poisoning narcotic drug other specified place
U205z00	[X]Intentional self-poisoning narcotic drug unspecified place
U206.00	[X]Intentional self-poisoning/exposure to hallucinogen
U206400	[X]Intentional self-poisoning hallucinogen in street/highway
U207.00	[X]Intentional self-poisoning/exposure to other autonomic drug
U207000	[X]Intentional self-poisoning/exposure to other autonomic drug at home
U207z00	[X]Intentional self-poisoning other autonomic drug unspecified place
U208.00	[X]Intentional self-poisoning/exposure to other/unspecified drug/ medicament
U208400	[X]Intentional self-poisoning other/unspecified drug/medication in street/highway
U208y00	[X]Intentional self-poisoning other/unspecified drug/medication other specified place
U208z00	[X]Intentional self-poisoning other/unspecified drug/medication unspecified place
U20A.00	[X]Intentional self-poisoning organic solvent
U20A.11	[X]Self-poisoning from glue solvent
U20A000	"[X]Intentional self-poisoning organic solvent
U20A400	"[X]Intentional self-poisoning organic solvent
U20Az00	"[X]Intentional self-poisoning organic solvent
U20B.00	[X]Intentional self-poisoning/exposure to other gas/vapour U20B.11 [X]Self carbon monoxide poisoning
U20B000	[X]Intentional self-poisoning/exposure to other gas/vapour at home
U20B200	[X]Intentional self-poisoning other gas/vapour school/public admin area
U20By00	[X]Intentional self-poisoning other gas/vapour other specified place
U20Bz00	[X]Intentional self-poisoning other gas/vapour unspecified place
U20C.00	[X]Intentional self-poisoning/exposure to pesticide
U20C.11	[X]Self-poisoning with weedkiller
U20C.12	[X]Self-poisoning with paraquat
U20C000	[X]Intentional self-poisoning/exposure to pesticide at home
U20Cy00	[X]Intentional self-poisoning pesticide other specified place
U20y.00	[X]Intentional self-poisoning/exposure to unspecified chemical
U20y000	[X]Intentional self-poisoning/exposure to unspecified chemical at home
U20y200	[X]Intentional self-poisoning unspecified chemical school/public admin area
U20yz00	[X]Intentional self-poisoning unspecified chemical unspecified place
U21.00	[X]Intentional self-harm by hanging/strangulation/suffocation
U210.00	[X]Intentional self-harm by hanging/strangulation/suffocation at home

U211.00	[X]Intentional self-harm by hanging/strangulation/suffocation occurrence at residential institution
U21y.00	[X]Intentional self-harm by hanging/strangulation/suffocation other specified place
U21z.00	[X]Intentional self-harm by hanging/strangulation/suffocation unspecified place
U22.00	[X]Intentional self-harm by drowning and submersion
U221.0	[X]Intentional self-harm by drowning/submersion occurrence at residential institution
U22y.00	[X]Intentional self-harm by drowning/submersion occurrence at other specified place
U22z.00	[X]Intentional self-harm by drowning/submersion occurrence at unspecified place
U24.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge
U241.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge occurrence at residential institution
U242.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge in school/public admin area
U25.00	[X]Intentional self-harm by other/unspecified firearm discharge
U250.00	[X]Intentional self-harm other/unspecif firearm discharge occurrence at home
U26.00	[X]Intentional self-harm by explosive material
U27.00	[X]Intentional self-harm by smoke
U270.00	[X]Intentional self-harm by smoke fire/flames occurrence at home
U274.00	[X]Intentional self-harm by smoke fire/flame occurrence in street/highway
U27z.00	[X]Intentional self-harm by smoke fire/flames occurrence in unspecified place
U28.00	[X]Intentional self-harm by steam hot vapours/hot objects
U280.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence at home
U28z.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence in unspecified place
U29.00	[X]Intentional self-harm by sharp object
U290.00	[X]Intentional self-harm by sharp object occurrence at home
U291.00	[X]Intentional self-harm by sharp object occurrence at residential institution
U294.00	[X]Intentional self-harm by sharp object occurrence in street/highway
U29y.00	[X]Intentional self-harm by sharp object occurrence at other specified place
U29z.00	[X]Intentional self-harm by sharp object occurrence at unspecified place
U2A.00	[X]Intentional self-harm by blunt object
U2A0.00	[X]Intentional self-harm by blunt object occurrence at home
U2A1.00	[X]Intentional self-harm by blunt object occurrence at residential institution
U2A3.00	[X]Intentional self-harm by blunt object occurrence at sports/athletic area
U2B.00	[X]Intentional self-harm by jumping from a high place
U2B0.00	[X]Intentional self-harm by jumping from high place occurrence at home
U2B4.00	[X]Intentional self-harm by jumping from high place occurring in street/highway
U2B6.00	[X]Intentional self-harm by jumping from high place industrial/construction area

U2By.00	[X]Intentional self-harm by jumping from high place occurrence other specified place
U2Bz.0	0
U2C.00	[X]Intentional self-harm by jumping/lying before moving object
U2C1.00	[X]Intentional self-harm by jumping/lying before moving object occurrence at residential institution
U2C4.00	[X]Intentional self-harm by jumping/lying before moving object occurrence in street/highway
U2Cy.00	[X]Intentional self-harm by jumping/lying before moving object occurrence other specified place
U2D.00	[X]Intentional self-harm by crashing of motor vehicle
U2D0.00	[X]Intentional self-harm by crashing of motor vehicle occurrence at home
U2D4.00	[X]Intentional self-harm by crashing of motor vehicle occurrence in street/highway
U2D6.00	[X]Intentional self-harm by crashing of motor vehicle occurrence industrial/construction area
U2E.00 [X]Self-mutilation	
U2y.00	[X]Intentional self-harm by other specified means
U2y0.00	[X]Intentional self-harm by other specified means occurrence at home
U2y1.00	[X]Intentional self-harm by other specified means occurrence at residential institution
U2yz.00	[X]Intentional self-harm by other specif means occurrence at unspecified place
U2z.00	[X]Intentional self-harm by unspecified means
U2z0.00	[X]Intentional self-harm by unspecified means occurrence at home
U2z2.00	[X]Intentional self-harm by unspecified means occurrence school/institution/public administrative area
U2zy.00	[X]Intentional self-harm by unspecified means occurrence other specified place
U2zz.00	[X]Intentional self-harm by unspecified means occurrence at unspecified place
U30.11	[X]Deliberate drug poisoning
U41.00	[X]Hanging strangulation + suffocation undetermined intent
U44.00	[X]Rifle shotgun + larger firearm discharge undetermined intent
U45.00	[X]Other + unspecified firearm discharge undetermined intent
U4B.00	[X]Falling jumping/pushed from high place undetermine intent
U4Bz.00	[X]Fall jump/push from high place undetermine intent occurring at unspecified place
U72.00	[X]Sequelae of intentional self-harm assault + event of undetermined intent
U720.00	[X]Sequelae of intentional self-harm
ZRLfC12	Health of the Nation Outcome Scales item 2 â€“ nonaccidental self-injury
ZX..00	Self-harm
ZX..11	Self-damage
ZX1.00	Self-injurious behaviour
ZX1.12	SIB â€“ self-injurious behaviour
ZX1.13	Deliberate self-harm
ZX11.00	Biting self

ZX11.11	Bites self
ZX12.00	Burning self
ZX13.00	Cutting self
ZX13.11	Cuts self
ZX15.00	Drowning self
ZX18.00	Hanging self
ZX19.00	Hitting self
ZX19100	Punching self
ZX19200	Slapping self
ZX1B.00	Jumping from height
ZX1B100	Jumping from building
ZX1B200	Jumping from bridge
ZX1B300	Jumping from cliff
ZX1C.00	Nipping self
ZX1E.00	Pinching self
ZX1G.00	Scratches self
ZX1H.00	Self-asphyxiation
ZX1H100	Self-strangulation
ZX1H200	Self-suffocation
ZX1I.00	Self-scalding
ZX1J.00	Self-electrocution
ZX1K.00	Self-incineration
ZX1K.11	Setting fire to self
ZX1K.12	Setting self alight
ZX1L.00	Self-mutilation
ZX1L100	Self-mutilation of hands
ZX1L200	Self-mutilation of genitalia
ZX1L300	Self-mutilation of penis
ZX1L600	Self-mutilation of ears
ZX1LD00	[X]Self mutilation
ZX1M.00	Shooting self
ZX1N.00	Stabbing self
ZX1Q.00	Throwing self in front of train
ZX1Q.11	Jumping under train
ZX1R.00	Throwing self in front of vehicle
ZX1S.00	Throwing self onto floor
ICD-10code	Description
X60	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics

	[hallucinogens], not elsewhere classified
X63	Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X65	Intentional self-poisoning by and exposure to alcohol
X66	Intentional self-poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours
X67	Intentional self-poisoning by and exposure to other gases and vapours
X68	Intentional self-poisoning by and exposure to pesticides
X69	Intentional self-poisoning by and exposure to other and unspecified chemicals and noxious substances
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X73	Intentional self-harm by rifle, shotgun and larger firearm discharge
X74	Intentional self-harm by other and unspecified firearm discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X77	Intentional self-harm by steam, hot vapours and hot objects
X78	Intentional self-harm by sharp object
X79	Intentional self-harm by blunt object
X80	Intentional self-harm by jumping from a high place
X81	Intentional self-harm by jumping or lying before moving object
X82	Intentional self-harm by crashing of motor vehicle
X83	Intentional self-harm by other specified means
X84	Intentional self-harm by unspecified means
Y10	Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent
Y12	Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent
Y13	Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent
Y15	Poisoning by and exposure to alcohol, undetermined intent
Y16	Poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours, undetermined intent
Y17	Poisoning by and exposure to other gases and vapours, undetermined intent
Y18	Poisoning by and exposure to pesticides, undetermined intent
Y19	Poisoning by and exposure to other and unspecified chemicals and noxious substances, undetermined intent
Y20	Hanging, strangulation and suffocation, undetermined intent

Y21	Drowning and submersion, undetermined intent
Y22	Handgun discharge, undetermined intent
Y23	Rifle, shotgun and larger firearm discharge, undetermined intent
Y24	Other and unspecified firearm discharge, undetermined intent
Y25	Contact with explosive material, undetermined intent
Y26	Exposure to smoke, fire and flames, undetermined intent
Y27	Contact with steam, hot vapours and hot objects, undetermined intent
Y28	Contact with sharp object, undetermined intent
Y29	Contact with blunt object, undetermined intent
Y30	Falling, jumping or pushed from a high place, undetermined intent
Y31	Falling, lying or running before or into moving object, undetermined intent
Y32	Crashing of motor vehicle, undetermined intent
Y33	Other specified events, undetermined intent
Y34	Unspecified event, undetermined intent

Appendix C. Covariates Forced into the High Density Propensity Score

All covariates assessed in the 365 days prior to study index date
Age at index date
Alcohol Abuse [Never, Former, Current, Unknown]
BMI
Duration of treated diabetes [time between first oral antidiabetic drug and study index date]
History of: Cirrhosis Congestive heart failure Hypertension Hyperlipidemia Ischemic heart disease Peripheral heart disease
Number of hospitalizations
Most recent HbAlc value to index date
Number of distinct prescription drugs
Prior use of benzodiazepines or other hypnotics, antipsychotics, levothyroxine or triiodothyrinine, anticonvulsants, or mood stabilizers
Sex
Smoking status [Never, Former, Current, Unknown]
Socioeconomic status [quintiles of Index of Mulitiple Deprivation]
Use of other antidiabetic agents
Year of cohort entry

Appendix D. Measures of frequency and association for depression among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6207	22218		502	16728
Person-years follow-up	5591	18683		549	13628
Number of events	45	215		10	182
Incidence per 1000 person-years (95%CI)	8.0 (6.0-10.8)	11.5 (10.1-13.2)		18.2 (10-33.5)	13.4 (11.6-15.4)
Crude Hazard Ratio (95% CI)	0.70 (0.50-0.96)	-ref-		1.39 (0.74-2.63)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.57-1.14)	-ref-		1.22 (0.61-2.42)	-ref-

S = suppressed due to low number of events

Appendix E. Measures of frequency and association for self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6211	22180		502	16632
Person-years follow-up	5632	18839		563	13696
Number of events	S	5		S	S
Incidence per 1000 person-years (95%CI)	S	0.3 (0.1-0.6)		S	S
Crude Hazard Ratio (95% CI)	0.66 (0.08-5.69)	-ref-		S	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.07-8.21)	-ref-		S	-ref-

S = suppressed due to low number of events

Appendix F. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are matched 1:1 by propensity score.

	DPP4i	SU		GLP1ra	SU
Number of patients	6008	6008		488	488
Person-years follow-up	548	4488		529	349
Number of events	44	49		10	7
Incidence per 1000 person-years (95%CI)	8.0 (6-10.8)	10.9 (8.3-14.4)		18.9 (10.4-34.8)	20.1 (9.9-41.3)
Crude Hazard Ratio (95% CI)	0.75 (0.50-1.13)	-ref-		0.99 (0.37-2.61)	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.51-1.16)	-ref-		0.98 (0.36-2.61)	-ref-

Appendix G. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are adjusted for pattern of glucose-lowering therapy.

	DPP4i	SU		GLP1RA	SU
Number of patients	4416	15943		117	4165
Person-years follow-up	3743	12614		90	3327
Number of events	36	140		S	61
Incidence per 1000 person-years (95%CI)	9.6 (7-13.3)	11.1 (9.4-13.1)		33.4 (12.1-97.5)	18.3 (14.3-23.6)
Crude Hazard Ratio (95% CI)	0.86 (0.60-1.24)	-ref-		1.82 (0.57-5.80)	-ref-
Adjusted Hazard Ratio (95% CI)	1.00 (0.66-1.49)	-ref-		1.55 (0.46-5.18)	-ref-

S = suppressed due to low number of events

Appendix H. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to only those with HES/ONS linked data.

	DPP4i	SU		GLP1ra	SU
Number of patients	3348	13243		262	9997
Person-years follow-up	2841	10762		290	7904
Number of events	27	132		S	111
Incidence per 1000 person-years (95%CI)	9.5 (6.5-13.8)	12.3 (10.3-14.5)		13.8 (5.6-35.3)	14 (11.7-16.9)
Crude Hazard Ratio (95% CI)	0.78 (0.51-1.17)	-ref-		1.00 (0.37-2.72)	-ref-
Adjusted Hazard Ratio (95% CI)	0.99(0.63-1.55)	-ref-		0.93 (0.32-2.71)	-ref-

Appendix I. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to second-line therapy after metformin monotherapy.

	DPP4i	SU		GLP1ra	SU
Number of patients	1255	4612		65	2112
Person-years follow-up	1191	3601		47	1680
Number of events	11	48		S	29
Incidence per 1000 person-years (95%CI)	9.2 (5.2-16.5)	13.3 (10.1-17.7)		43(13.3-155.3)	17.3 (12-24.8)
Crude Hazard Ratio (95% CI)	0.71 (0.37-1.38)	-ref-		2.49(0.59-10.45)	-ref-
Adjusted Hazard Ratio (95% CI)	0.67 (0.34-1.34)	-ref-		1.92(0.44-8.31)	-ref-

S = suppressed due to low number of events

Appendix J. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when BMI categories (in addition to hdps deciles) were added to the Cox proportional regression model.

	DPP4i	SU		GLP1ra	SU
Number of patients	6206	22128		501	16409
Person-years follow-up	5589	18596		549	13418
Number of events	46	218		10	183
Incidence per 1000 person-years (95%CI)	8.2 (6.2-11)	11.7 (10.3-13.4)		18.2 (10-33.5)	13.6 (11.8-15.8)
Crude Hazard Ratio (95% CI)	0.70 (0.51-0.96)	-ref-		1.36 (0.72-2.58)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.58-1.15)	-ref-		1.25 (0.63-2.51)	-ref-

S = suppressed due to low number of events

Appendix K. Time-dependent Cox regression for DPP-4 inhibitor monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
DPP-4i monotherapy	-0.07	0.93	0.65	1.32	0.18	0.69
DPP-4i/SU	-0.53	0.59	0.34	1.02	0.28	0.06
DPP-4i/Other	-0.16	0.85	0.70	1.04	0.10	0.11
DPP-4i/SU/Other	-0.13	0.88	0.68	1.14	0.13	0.33

*Adjusted for deciles of hdps

Appendix L. Time-dependent Cox regression for GLP-1 receptor agonist (GLP1ra) monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
GLP1ra monotherapy	-0.51	0.60	0.30	1.21	0.36	0.15
GLP1ra /SU	0.45	1.57	0.78	3.18	0.36	0.21
GLP1ra /Other	0.14	1.16	0.88	1.52	0.14	0.31
GLP1ra /SU/Other	-0.31	0.73	0.47	1.15	0.23	0.18

*Adjusted for deciles of hdps

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Cohort in title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Structured abstract provided**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Introduction – paragraphs 1 and 2**
Objectives	3	State specific objectives, including any prespecified hypotheses **Introduction – paragraph 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Methods, Study Design and Data Sources section, paragraph 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods, Study Design and Data Sources section, paragraph 1**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Methods, Study Cohort section, paragraph 1**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Methods, Exposure and Outcome Definitions section**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Methods, Exposure and Outcome Definitions section** **Supplemental appendix**
Bias	9	Describe any efforts to address potential sources of bias **Methods, Statistical Analysis section, paragraphs 2 and 3**
Study size	10	Explain how the study size was arrived at **Figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Methods, Exposure and Outcome Definitions section** **Methods, Statistical Analysis section**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Methods, Statistical Analysis section**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) **Table 3** **Results section**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Table 3** **Results section** **Supplemental appendix**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Results section** **Table 3**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Results section, paragraph 5** **Figure 2** **Figure 3** **Supplemental appendix**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Discussion section, paragraph 1**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Discussion section, paragraph 5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Discussion section, final paragraph**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding support**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

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BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023830.R1
Article Type:	Research
Date Submitted by the Author:	14-Aug-2018
Complete List of Authors:	Gamble, John Michael; University of Waterloo, School of Pharmacy; Memorial University of Newfoundland, School of Pharmacy Chibrikov, Eugene; Memorial University of Newfoundland, School of Pharmacy and Faculty of Medicine; University of Waterloo, School of Pharmacy Midodzi, William; Memorial University of Newfoundland, Faculty of Medicine Twells, Laurie; Memorial University of Newfoundland, School of Pharmacy and Faculty of Medicine Majumdar, Sumit; University of Alberta, Department of Medicine
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Depression & mood disorders < PSYCHIATRY, cohort study, pharmacoepidemiology

Examining the Risk of Depression or Self-Harm Associated with Incretin-based Therapies Used to Manage Hyperglycemia in Patients with Type 2 Diabetes: A Cohort Study Using the UK Clinical Practice Research Datalink

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Abbreviated Title: Depression and Self-Harm Among Incretin-based Therapy Users

Key terms: cohort study, type 2 diabetes, dipeptidyl-peptidase 4 inhibitors, glucagon-like receptor 1 agonists, depression, suicide, self-harm

Counts: Abstract=290; Manuscript= 3079; Figures=3; Tables=3; References=45

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Abstract

Objectives: To compare population-based incidence rates of new-onset depression or self-harm in patients initiating incretin-based therapies with that of sulfonylureas (SU) and other glucose-lowering agents.

Design: Population-based cohort study

Setting: Patients attending primary care practices registered with the UK-based Clinical Practice Research Datalink (CPRD).

Participants: Using the UK-based Clinical Practice Research Datalink (CPRD), we identified two incretin-based therapies cohorts: (1) DPP-4i-cohort, consisting of new-users of DPP-4 inhibitors and sulfonylureas, and (2) GLP-1RA-cohort, consisting of new-users of GLP-1 receptor agonists and sulfonylureas, between Jan-2007 and Jan-2016. Patients with a prior history of depression, self-harm, and other serious psychiatric conditions were excluded.

Main outcome measures: The primary study outcome comprised a composite of new-onset depression or self-harm. Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Deciles of high-dimensional propensity scores and concurrent number of glucose-lowering agents were used to adjust for potential confounding.

Results: We identified new-users of 6206 DPP-4i and 22128 sulfonylureas in the DPP-4i-cohort, and 501 GLP-1RA and 16409 sulfonylurea new-users in the GLP-1RA-cohort. The incidence of depression or self-harm was 8.2 vs. 11.7 events/1000-person-years in the DPP-4i-cohort and 18.2 vs. 13.6 events/1000-person-years in the GLP-1RA-cohort for incretin-based therapies vs sulfonylureas, respectively. Incretin-based therapies were not associated with an increased or decreased incidence of depression or self-harm compared to sulfonylureas (DPP-4i-cohort: unadjusted hazard ratio (HR) 0.70, 95% confidence internal (CI): 0.51-0.96) adjusted HR 0.80, 95% CI: 0.57-1.13; GLP-1RA-cohort: unadjusted hazard ratio (HR) 1.36, 95% confidence internal (CI): 0.72-2.58; adjusted HR 1.25, 95% CI: 0.63-2.50). Consistent results were observed for other glucose-lowering comparators including insulin and thiazolidinediones.

Conclusions: Our findings suggest that the two incretin-based therapies are not associated with an increased or decreased risk of depression or self-harm.

Strengths and limitations of the study

- Incretin-based therapies, dipeptidyl peptidase-4 inhibitors [DPP-4i] and glucagon-like peptide-1 receptor agonists [GLP-1RA], used to manage hyperglycemia in patients with type 2 diabetes may have neuropsychiatric effects due to GLP-1 receptor expression in the central nervous system
- This study found that initiation of an incretin-based therapy, either a DPP-4 inhibitor or a GLP-1RA, does not appear to substantially increase or decrease the risk of depression or self-harm in patients with type 2 diabetes
- This study used a new-user active comparator design with high dimensional propensity scores to control for confounding
- This study cannot rule out small or modest difference in risk of depression or self-harm between incretin-based therapy users and other glucose-lowering due to study power limitations

Introduction

Patients with diabetes frequently have coexisting depression with a prevalence ranging from 12% to 27%.[1] Depression is not only associated with diabetes but with an increased risk of diabetes-related complications,[2] decreased quality of life,[3] and decreased life-expectancy.[4] Diabetes is also associated with new-onset depression; however, the temporal association between diabetes and depression remains unclear.[5,6] Moreover, diabetes is associated with an increased risk of intentional self-harm,[7,8] albeit there is significant heterogeneity between studies assessing the association between diabetes and suicide.[9] It has been postulated that certain glucose-lowering pharmacotherapies may have a positive influence on the symptoms of depression, although the evidence is sparse.[10–15] The incretin-based therapies in particular may have neuropsychiatric effects given the presence of glucagon-like peptide-1 (GLP-1) receptors in the central nervous system.[16,17]

Concerns surrounding central nervous system effects stem from a case report of exenatide-induced depression and from pooled adverse event data from pre-marketing clinical trials for sitagliptin.[18–20] Pooled event rates for the latter suggested a 4-fold increased risk of suicide ideation and completed suicide in sitagliptin users compared to non-users.[19,21] Animal models suggest adverse neuropsychiatric effects are biologically plausible given the expression of GLP-1 receptors in the brain.[20] Furthermore, studies have

shown low dipeptidyl peptidase-4 (DPP-4) activity is correlated with depression.[22–24] Although the case-report mentioned above suggested a potential increased risk of depression, a recent study reported positive effects of GLP-1 receptor agonists on patients well-being.[25] Therefore alternations in DPP-4 enzymatic activity may modulate the pathophysiology of neuropsychiatric conditions such as major depression.

Using data from a population-based cohort of patients with type 2 diabetes, we aimed to quantify the association between incretin-based therapies and the composite of new-onset depression and self-harm.

Methods

Study Design and Data Sources

We conducted a population-based cohort study using data from the Clinical Practice Research Datalink (CPRD), which captures electronic medical information for primary care encounters by general practitioners in the United Kingdom (UK).[26] The CPRD contains de-identified individual-level longitudinal data collected from a subset of primary care practices (~700) in the UK. The CPRD data is a representative sample that is similar to the overall UK population in age, sex, and ethnicity.[27] The database includes sociodemographic and lifestyle variables (e.g., alcohol consumption), physiological measures (e.g., blood pressure), laboratory testing (e.g., glycated hemoglobin [A1c]), physician-assigned diagnoses using the Read classification system, and prescription records from general practitioner records. Data quality checks are performed in accordance with standardized guidelines that certify practices as up-to-standard. Furthermore, over 350 validation studies have been performed using the CPRD.[28,29] Information on hospitalizations and causes of death are available for a subset of CPRD patients through linkages with the external databases. Details regarding the data quality, linkages, and utility are available elsewhere.[30] The CPRD has been used extensively to study associations between drugs and depression and self-harm.[31–35] Our study protocol was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA, August 2017) and received approval from the Health Research Ethics Board at Memorial University.

Study Cohorts

Our source population consisted of all patients over 18 years of age with a minimum of 12-months of up-to-standard medical history in the CPRD database that received a new diagnosis for type 2 diabetes or a new prescription for any glucose-lowering therapy between January 1, 2001 and the February 2016 CPRD dataset build. We used a 365-day washout period to define a new diagnosis or new glucose-lowering therapy use. A sub-cohort of patients (~58%) selected from the source population was linked to Hospital Episode Statistics (HES – follow-up until 31March2014), Office of National Statistics (ONS – follow-up until 30April2014), and index of multiple deprivation (IMD [2010]) data to capture hospital records, causes of death, and socioeconomic status information, respectively. Women with polycystic ovarian syndrome, gestational diabetes, or whom were pregnant during the study period were

excluded. In addition, we excluded patients with a study entry date prior to January 1, 2007 as the first incretin-based therapies became available in the UK in early 2007.

We identified two main study cohorts. Specifically, the first cohort consisted of new-users of DPP-4 inhibitors and new-users of sulfonylureas (DPP-4 inhibitor cohort) and the second cohort consisted of new-users of GLP-1 receptor agonists and new-users of sulfonylureas (GLP-1 receptor agonist cohort). Although new-users of sulfonylureas served as the reference population for both cohorts, these individuals were selected separately for each cohort as prior use of other non-incretin glucose-lowering agents was permitted. To minimize potential selection bias within the above cohorts, we excluded patients with a history of depression, self-harm, anxiety, and other serious psychiatric conditions in the year prior to a patient's cohort entry date.

Exposure and Outcome Definitions

Within each incretin-based therapy cohort, we defined person-time exposure to all classes of glucose-lowering therapy including (1) DPP-4 inhibitors, (2) GLP-1 receptor agonists, (3) Sulfonylureas, (4) Metformin, (5) Thiazolidinediones, (6) Sodium glucose co-transporter-2 inhibitors, (7) Meglitinides, (8) Acarbose, (9) Insulin, and (10) no glucose-lowering drug therapy (i.e. diet/lifestyle). Patient's contributed person-time to each of the aforementioned categories on the day of their first prescription or date of diagnosis (defined as the patient's index date) until a patient discontinued the drug, left a CPRD practice, died, or on the final date of follow-up, whichever occurred first. To account for potential non-adherence, we included a portion of follow-up time following the end of the expected medication supply that was equivalent to 50% of the prescription duration as a period of exposure.

Our primary outcome the composite of either new-onset depression or self-harm, including suicide and suicidal ideation. If a patient experienced more than one event, the date of the first event was used. New-onset depression or episodes of self-harm were identified using diagnostic codes from either the CPRD, HES, or ONS data sources (specific codes available in supplemental material in Appendices A and B).

Statistical Analysis

Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Our primary exposure contrasts of interest were DPP-4 inhibitors vs. sulfonylureas and GLP-1 receptor agonists vs. sulfonylureas within the DPP-4 inhibitor and GLP-1 receptor agonists cohorts respectively. Sulfonylureas were chosen a priori as the main reference group given their use in clinical practice as second or third agents resembles incretin-based therapies. Patients contributed follow-up time from the initiation of the incretin-based therapy of interest or comparator until they experienced the composite outcome of interest or were censored. Censoring occurred upon the earliest date of the following events: discontinuation of the incretin-based therapy of interest or comparator, switching between an incretin-based therapy to the comparator (or vice-versa), leaving a CPRD practice site, death, end of study period.

To adjust for potential confounders, we used a high-dimensional propensity score (hdPS) algorithm to select up to 40 empirical covariates.[36] Using a multivariable logistic regression model that included the both empirically derived and predefined (age, sex, alcohol abuse, body mass index, duration of treated diabetes, comorbidities, number of hospitalizations, HbA1c, prior medications use, smoking status, socioeconomic status [quintiles of the index of multiple deprivation], use of other glucose-lowering therapies, year of cohort entry. A detailed list of covariates forced into propensity score model is shown in Appendix C) covariates, we calculated the probability of initiating a DPP-4 inhibitor versus a sulfonylurea (or comparator for sensitivity analysis). Patients with overlapping propensity scores were included in the analysis. A separate hdPS procedure was run for the GLP-1 receptor agonist cohort. Adjusted hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards regression model with deciles of the hdPS and variable indicating the number of glucose-lowering agents during follow-up (1, 2, 3 or more). We used standard graphical approaches to assess model assumptions for which no violations were noted.

Secondary analyses included alternative comparator groups and components of composite outcome (i.e., depression and self-harm as separate outcomes). In addition, we conducted several additional sensitivity analyses. First, we used two alternative methods to adjust for potential confounding including a matched propensity score approach (1:1 -

matching using greedy nearest neighbor approach with a caliper set at 0.2 times the standard deviation of the natural logarithm of the propensity score) and grouping patients with identical patterns of glucose-lowering therapies prior to and following cohort initiation. For the latter approach, an example of how we grouped patients is as follows. Patients who started with metformin monotherapy and added an incretin-based therapy would be grouped with patients who also started metformin monotherapy and then added the comparator drug of interest. Groups with less than 25 patients were excluded from this analysis. We used a categorical variable to adjust for all groups within our multivariable Cox proportional hazards model. Second, we ran several analyses using restricted cohorts including restricting our cohort to patients eligible for HES/ONS linkage (i.e., patients with hospital and death certificate records), restricting to monotherapy users, restricting to a cohort of metformin monotherapy users who added the incretin-based therapy of interest or a sulfonylurea. Third, we added BMI (as a categorical variable) to Cox proportional hazards model given that weight may be a confounding factor.[37,38] Fourth, we used time-dependent variables to classify our exposures of interest throughout follow-up time. All analyses were conducted with R version 3.3.3.

Patient and Public Involvement

No patients were involved in any aspect of the study.

Results

DPP-4 Inhibitor Cohort

Within the DPP-4 inhibitor new user cohort, there were 6206 initiators of a DPP-4 inhibitor and 22128 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 324 (362) days for DPP-4 inhibitor users and 299 (385) days for sulfonylurea users. Compared to sulfonylurea users, DPP-4 inhibitor users were on average younger, had fewer hospitalizations in the year prior to cohort entry, and less likely to have impaired kidney function. Patient characteristics were well-balanced following propensity score matching (Table 1). There were a total 264 patients identified with new-onset depression or self-harm.

The incidence of depression or self-harm was 8.2 per 1000 person-years in DPP-4 inhibitor users compared to 11.7 per 1000 person-years in sulfonylurea users (unadjusted

hazard ratio (HR): 0.70 95% confidence interval (CI) 0.51-0.96 [table 2]). Similarly, the crude incidence rates were smaller for DPP-4 inhibitor users versus other comparators (10.0 vs. 10.8 per 1000 person-years for TZDs; 9.8 vs. 20.7 for insulin users). However, following adjustment for potential confounding variables, there was no significant association between DPP-4 inhibitor use and the risk of depression or self-harm for all comparator groups (sulfonylurea comparator: adjusted HR 0.80, 95% CI 0.57-1.13; TZD comparator: adjusted HR 1.17, 95% CI 0.70-1.96; insulin comparator: adjusted HR 0.98, 95% CI 0.53-1.83). Appendices D and E show the results for the risks of depression and self-harm separately.

GLP-1 Receptor Agonist Cohort

Within the GLP-1 receptor agonist cohort, there were 501 initiators of a GLP-1 receptor agonist and 16409 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 397 (409) days for GLP-1 receptor agonist users and 292 (373) days for sulfonylurea users. Compared to sulfonylurea users, GLP-1 receptor agonist users were on average younger, more likely female, used more drugs in the year prior to cohort entry, had a lower baseline HbA1c, more likely to have used several medications prior to cohort entry including insulin, SSRIs, or other antidepressant. Following propensity score matching, baseline patient characteristics were well-balanced (Table 3). There were a total 193 patients identified with new-onset depression or self-harm.

The incidence rate of depression or self-harm was non-significantly higher for GLP-1 receptor users compared to sulfonylurea users (18.2 vs. 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72-2.58; adjusted HR 1.25, 95% CI 0.63-2.50), TZDs (16.4 vs. 12.5 per 1000 person-years; unadjusted HR 1.32, 95% CI 0.72-2.42; adjusted HR 1.18. 95% CI 0.53-2.65), and insulin users (13.6 vs. 20.7 per 1000 person-years; unadjusted HR 0.74, 95% CI 0.35-1.56; adjusted HR 1.07, 95% CI 0.39-2.94). All measured associations remained non-significant following adjustment for potential confounders (Table 2). Appendix D shows the results for depression analyzed as a separate outcome. We were unable to analyze results for self-harm separately, due to small numbers of events (Appendix E).

Sensitivity Analyses

Figures 2 and 3 provide the number of events per treatment exposure group and measures of association for selected sensitivity analyses across the main DPP-4 inhibitor and

GLP-1 receptor agonist cohorts. There were too few events to run a stable statistical model for all pre-specified sensitivity analyses (e.g. new monotherapy users); however, findings from models that were run were consistent with our main results suggesting that DPP-4 inhibitor use did not have an increased or decreased risk of new-onset depression (Appendix F to L).

Discussion

New users of DPP-4 inhibitors and new users of GLP-1 receptor agonists did not have an increased or decreased risk of a new diagnosis of depression or episode of self-harm. These findings extend our current knowledge regarding the relative safety of the incretin-based therapies used to manage hyperglycemia in patients with type 2 diabetes.

The impetus for our study was the safety signal generated by randomized controlled trials and a case-report suggesting that incretin-based therapies may affect the risk of depression or self-harm. Specifically, early trial data found a 4-times greater risk of suicidal ideation or completed suicide in sitagliptin users vs glipizide users.[19,21] A higher incidence of depression was also observed in the long-term safety population among phase-3 clinical trial in sitagliptin 100mg users (13/429) compared to placebo (0/154); however, the incidence of psychiatric events was no different among pooled phase 3 studies (3.0% in sitagliptin 100mg users; 2.4% in sitagliptin 200mg users, and 3.2% in placebo users).[20] Moreover, a case-report has also been published regarding exenatide-induced depression.[18]

Despite our findings suggesting a lack of association between incretin-based agents and depression or self-harm, there is a substantial evidence-base from animal models that suggest incretin-based therapies may affect mood disorders. Anderberg and colleagues found differential effects of acute versus chronic exposure to a GLP-1 receptor agonist.[39] Acute activation of GLP-1 receptors was associated with anxiogenic effects, whereas chronic GLP-1 receptor activation did not elicit anxiogenic effects in Sprague-Dawley rats. In fact, chronic exposure to a GLP-1 receptor agonist was associated with a decrease in depressive-like behavior. Furthermore, acute stimulation of GLP-1 receptors affected serotonin turnover and serotonin receptor expression in the amygdala; however, chronic stimulation did not affect serotonin turnover or receptor expression. In addition to effects on serotonin, activation of GLP-1 may have mood effects through impacting central dopamine levels.[40] A mice model suggests that liraglutide, a GLP-1 receptor agonist, has antipsychotic properties possibly

through its affecting dopamine activity in the brain.[41] Interestingly, the DPP-4 inhibitor sitagliptin, did not exhibit the same antipsychotic properties.

Another possible mechanism by which glucose lowering therapies may affect mood disorders is through the reduction in inflammatory cytokines/mediators. Moulton et al reported improvement in depressive symptoms over 1-year in a cohort of 1735 newly diagnosed patients with type 2 diabetes.[10] The improvement in depressive symptoms measure by the PHQ-9 was independent of change in glycemic control and was correlated with a change in the inflammatory marker hs-CRP. Furthermore, a meta-analysis found that pioglitazone was associated with a reduction in symptoms of depression compared to placebo (pooled odds ratio = 3.3, 95% confidence interval 1.4 to 7.8).[11] A 12-week open-label study also found that pioglitazone was associated with a reduction in depression symptoms as well as a decrease in c-reactive protein and decreased insulin resistance.[12] Indeed, a population-based cross-sectional study found that numerous inflammatory markers (e.g., c-reactive protein, inerleukin-1 receptor agonist, monocyte chemotactic protein-1, white blood cell count, triglyceride) were associated with depression in patients with type 2 diabetes.[42] To further test this hypothesis among DPP-4 inhibitor users, there is an ongoing small clinical trial evaluating the effect of sitagliptin on symptoms of depression in the elderly (EudraCT Number: 2015-004527-32).[43]

Our study is subject to the standard limitations of observational cohort studies including the potential for residual and unmeasured confounding. Although we adjusted for over 70 potential confounders using an HdPS approach, we were not able to capture all relevant potential confounders such as severity of depressive symptoms and patient level socioeconomic status. Our follow-up time was also limited (DPP-4 cohort mean follow-up time = 305 days; GLP-1 receptor agonist cohort mean follow-up = 296 days), therefore, it is possible that a longer time frame was required to detect an association. However, it would be expected that an effect on depression symptoms mediated by serotonin or dopaminergic central pathways would be apparent after 4 to 6 weeks or sooner. There were a limited number of self-harm events and our study was not powered to detect clinically relevant differences across exposure groups for this component of our composite outcome. Similarly, given the lower and upper limits of the 95% confidence intervals, our study cannot rule out small or moderate differences in the risk of depression across exposure groups. Misclassification of the exposure or outcome variables of interest may have also impacted our

findings. Our exposure variables of interest (incretin-based therapies) were measured based on primary care prescription records and therefore may overestimate true exposure due to primary and secondary non-adherence. In addition, prescriptions written by specialists are not captured in the CPRD. It is possible that when the incretin-based therapies were introduced they were more frequently prescribed by specialists and our study would miss the initial prescription, however, subsequent prescriptions written by general practitioners would be captured. Previous studies have shown that depression is likely underestimated using diagnostic codes, although positive predictive values have generally been greater than 90% using ICD-10 codes.[44] Under-ascertainment of depression would likely be non-differential between our exposure groups of interest and therefore bias our findings toward the null. Suicide and self-harm have also been shown to be underestimated using CPRD data and the use of linked mortality data via the Office of National Statistics improves the sensitivity for capturing suicide and self-harm; however, underreporting of events is still expected.[45] In addition, the role of incretin-based agents may have shifted over time whereby when they were first introduced to the market were not used commonly as 2nd line agents and sulfonylureas may have been used as first or second-line agents. We attempted to control for both temporal trends and timing of therapy by using calendar time, duration of and prior exposure of glucose-lowering therapies as covariates in the propensity score.

Our findings provide some reassurance regarding the safety of the incretin-based therapies in the treatment of type 2 diabetes. Specifically, our study results suggest that there is not a clinically relevant association between either DPP-4 inhibitors or GLP-1 receptor agonists and depression or self-harm.

Authors' Contributions: JMG, EC, WKM, LKT and SRM, were involved in the concept and design of the study. JMG was responsible for drafting the first version of the manuscript. All authors contributed to the interpretation of data. JMG, EC, WKM, and LKT provided revisions to the manuscript. JMG will act as guarantor for the study.

Acknowledgements: JMG is supported as a New Investigator Award from the Canadian Institute of Health Research and a Clinician Scientist Award from Diabetes Canada. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the author/s alone.

Funding Support: This work was supported by an operating grant from the Canadian Institute for Health Research (FRN173599 – 287647).

Competing Interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships that may be relevant to the submitted work; and no other relationships or activities that could appear to have influence the submitted work.

Ethical approval: This study was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA) and received approval from the Health Research Ethics Board at Memorial University.

located; and, vi) licence any third party to do any or all of the above.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing: no additional data available.

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TABLES

Table 1. Patient Characteristics of New-user DPP-4 Inhibitor Cohort Before and After Propensity Score Matching. and GLP-1 Receptor Agonist Cohorts.

	DPP4 Inhibitor New User Cohort Before Propensity Score Matching		DPP4 Inhibitor New User Cohort After Propensity Score Matching	
	DPP-4i (n=6206)	SU (n=22128)	DPP-4i (n=6008)	SU (n=6008)
Age in yrs (sd)	58(12.2)	60.5(13.8)	58.1(12.2)	58.2(12.5)
Female	2258(36.4%)	8107(36.6%)	2189(36.4%)	2187(36.4%)
Measure of deprivation				
Least	624(10.1%)	2492(11.3%)	603(10%)	594(9.9%)
Most	615(9.9%)	2342(10.6%)	603(10%)	614(10.2%)
Unknown	2862(46.1%)	8780(39.7%)	2739(45.6%)	2683(44.7%)
Diabetes duration in yrs (sd)	2.0(1.8)	1.0(1.5)	1.9(1.7)	1.9(1.8)
Body Mass Index >30	4162(67.1%)	10661(48.2%)	3994(66.5%)	3978(66.2%)
Number of hospitalizations in year prior to cohort entry				
0	5647(91%)	18516(83.7%)	5452(90.7%)	5470(91%)
1	378(6.1%)	2105(9.5%)	375(6.2%)	379(6.3%)
2	109(1.8%)	784(3.5%)	109(1.8%)	92(1.5%)
3+	72(1.2%)	723(3.3%)	72(1.2%)	67(1.1%)
Number of drugs in year prior to cohort entry				
0-4	721(11.6%)	3098(14%)	703(11.7%)	671(11.2%)
5-10	3204(51.6%)	10379(46.9%)	3081(51.3%)	3119(51.9%)
11+	2281(36.8%)	8651(39.1%)	2224(37%)	2218(36.9%)
HbA1c				
<6.5%	242(3.9%)	1393(6.3%)	238(4%)	233(3.9%)
6.5-7.5%	1104(17.8%)	3349(15.1%)	1049(17.5%)	1053(17.5%)
7.5-9%	2831(45.6%)	7121(32.2%)	2701(45%)	2694(44.8%)
9%+	2000(32.2%)	9833(44.4%)	1991(33.1%)	2007(33.4%)
Unknown	29(<1%)	432(2%)	29(<1%)	21(<1%)
e*GFR* <60	883(14.2%)	4429(20%)	857(14.3%)	890(14.8%)
Diagnoses in year prior to cohort entry				
Heart Failure	68(1.1%)	369(1.7%)	68(1.1%)	51(<1%)
Hypertension	1095(17.6%)	4475(20.2%)	1066(17.7%)	1087(18.1%)
Dyslipidemia	213(3.4%)	1093(4.9%)	213(3.5%)	212(3.5%)
Ischemic heart	174(2.8%)	1033(4.7%)	171(2.8%)	168(2.8%)
Peripheral vascular	25(<1%)	145(<1%)	25(<1%)	24(<1%)
Prescription drug use in year prior to cohort entry				
Metformin	5775(93.1%)	16534(74.7%)	5578(92.8%)	5638(93.8%)
Acarbose	S	8(<1%)	S	S
SGLT2 inhibitors	38(<1%)	93(<1%)	38(<1%)	40(<1%)
Meglitinide	47(<1%)	39(<1%)	38(<1%)	29(<1%)
Thiazolidinedione	252(4.1%)	403(1.8%)	222(3.7%)	209(3.5%)
Insulin	82(1.3%)	331(1.5%)	80(1.3%)	86(1.4%)
Hypnotic	332(5.3%)	1486(6.7%)	328(5.5%)	324(5.4%)
Mood	85(1.4%)	280(1.3%)	81(1.3%)	83(1.4%)
Anticonvulsant	271(4.4%)	832(3.8%)	260(4.3%)	266(4.4%)
Antipsychotics	176(2.8%)	829(3.7%)	172(2.9%)	171(2.8%)

S = suppressed due to low number of events

Table 2. Measures of frequency and association for depression or self-harm in new-users of DPP-4 Inhibitors (DPP4i) or new-users of GLP-1 receptor agonists (GLP1ra) vs. sulfonylureas (SU), thiazolidinediones (TZD), or insulin.

	DPP4 Inhibitor New User Cohort		GLP1 Receptor Agonist New User Cohort	
COMPARATOR: SU				
	DPP4i	**SU**	**GLP1ra**	**SU**
Number of patients	6206	22128	501	16409
Person-years of follow-up	5589	18596	549	13418
Number of Events	46	218	10	183
Incidence per 1000 person-years (95%CI)	8.2(6.2-11)	11.7(10.3-13.4)	18.2(10-33.5)	13.6(11.8-15.8)
Crude HR	0.70(0.51-0.96)	-ref-	1.36(0.72-2.58)	-ref-
Adjusted HR	0.80(0.57-1.13)	-ref-	1.25(0.63-2.50)	-ref-
COMPARATOR: TZD				
	DPP4i	**TZD**	**GLP1ra**	**TZD**
Number of patients	9565	2512	851	2011
Person-years of follow-up	9190	2786	1035	2165
Number of Events	92	30	17	27
Incidence per 1000 person-years (95%CI)	10.0(8.2-12.3)	10.8(7.6-15.4)	16.4(10.3-26.3)	12.5(8.6-18.1)
Crude HR	0.90(0.59-1.36)	-ref-	1.32(0.72-2.42)	-ref-
Adjusted HR	1.17(0.70-1.96)	-ref-	1.18(0.53-2.65)	-ref-
COMPARATOR: INSULIN				
	DPP4i	**Insulin**	**GLP1ra**	**Insulin**
Number of patients	10049	3600	854	2745
Person-years of follow-up	9878	1161	1033	919
Number of Events	97	24	14	19
Incidence per 1000 person-years (95%CI)	9.8(8.1-12)	20.7(13.9-30.8)	13.6(8.1-22.7)	20.7(13.3-32.3)
Crude HR	0.54(0.34-0.87)	-ref-	0.74(0.35-1.56)	-ref-
Adjusted HR	0.98(0.53-1.83)	-ref-	1.07(0.39-2.94)	-ref-

Table 3. Patient Characteristics of New-user GLP-1 Receptor Agonist Cohort Before and After Propensity Score Matching.

	GLP-1 Receptor Agonist New User Cohort Before Propensity Score Matching		GLP-1 Receptor Agonist New User Cohort After Propensity Score Matching	
	GLP-1RA (n=501)	**SU (n=16409)**	**GLP-1RA (n=488)**	**SU (n=488)**
Age in yrs (sd)	49.4(11.3)	57.8(12.9)	49.7(11.2)	49.2(12.6)
Female	204(40.7%)	6021(36.7%)	198(40.6%)	174(35.7%)
Measure of				
Least	40(8%)	1688(10.3%)	40(8.2%)	29(5.9%)
Most	56(11.2%)	1770(10.8%)	56(11.5%)	52(10.7%)
Unknown	240(47.9%)	6784(41.3%)	230(47.1%)	214(43.9%)
Diabetes duration in yrs (sd)	1.7(1.6)	1.2(1.6)	1.7(1.6)	1.7(1.8)
Body Mass Index>30	470(93.8%)	10481(63.9%)	458(93.9%)	452(92.6%)
Number of hospitalizations in year prior to cohort entry				
0	456(91%)	14170(86.4%)	445(91.2%)	437(89.5%)
1	29(5.8%)	1344(8.2%)	28(5.7%)	27(5.5%)
2	10(2%)	499(3%)	9(1.8%)	17(3.5%)
3+	6(1.2%)	396(2.4%)	6(1.2%)	7(1.4%)
Number of drugs in year prior to cohort entry				
0-4	17(3.4%)	1660(10.1%)	17(3.5%)	18(3.7%)
5-10	195(38.9%)	7899(48.1%)	192(39.3%)	208(42.6%)
11+	289(57.7%)	6850(41.7%)	279(57.2%)	262(53.7%)
HbA1c				
<6.5%	66(13.2%)	1085(6.6%)	62(12.7%)	66(13.5%)
6.5-7.5%	99(19.8%)	2593(15.8%)	97(19.9%)	99(20.3%)
7.5-9%	150(29.9%)	5357(32.6%)	145(29.7%)	134(27.5%)
9%+	179(35.7%)	7068(43.1%)	177(36.3%)	178(36.5%)
Unknown	7(1.4%)	306(1.9%)	7(1.4%)	11(2.3%)
e*GFR* <60	36(7.2%)	2821(17.2%)	35(7.2%)	40(8.2%)
Diagnoses in year prior to cohort entry				
Heart Failure	5(1%)	244(1.5%)	5(1%)	6(1.2%)
Hypertension	107(21.4%)	3398(20.7%)	106(21.7%)	104(21.3%)
Dyslipidemia	16(3.2%)	771(4.7%)	16(3.3%)	23(4.7%)
Ischemic heart	11(2.2%)	644(3.9%)	11(2.3%)	9(1.8%)
Peripheral	S	106(<1%)	S	S
Prescription drug use in year prior to cohort entry				
Metformin	457(91.2%)	13542(82.5%)	445(91.2%)	449(92%)
Acarbose	2(<1%)	7(<1%)	1(<1%)	1(<1%)
SGLT2 inhibitors	5(1%)	87(<1%)	5(1%)	5(1%)
Meglitinide	11(2.2%)	39(<1%)	10(2%)	10(2%)
Thiazolidinedione	38(7.6%)	376(2.3%)	38(7.8%)	41(8.4%)
Insulin	65(13%)	307(1.9%)	55(11.3%)	59(12.1%)
Hypnotic	32(6.4%)	1093(6.7%)	32(6.6%)	35(7.2%)
Mood	10(2%)	228(1.4%)	10(2%)	8(1.6%)
Anticonvulsant	33(6.6%)	682(4.2%)	31(6.4%)	32(6.6%)
Antipsychotics	12(2.4%)	507(3.1%)	**12(2.5%)**	12(2.5%)

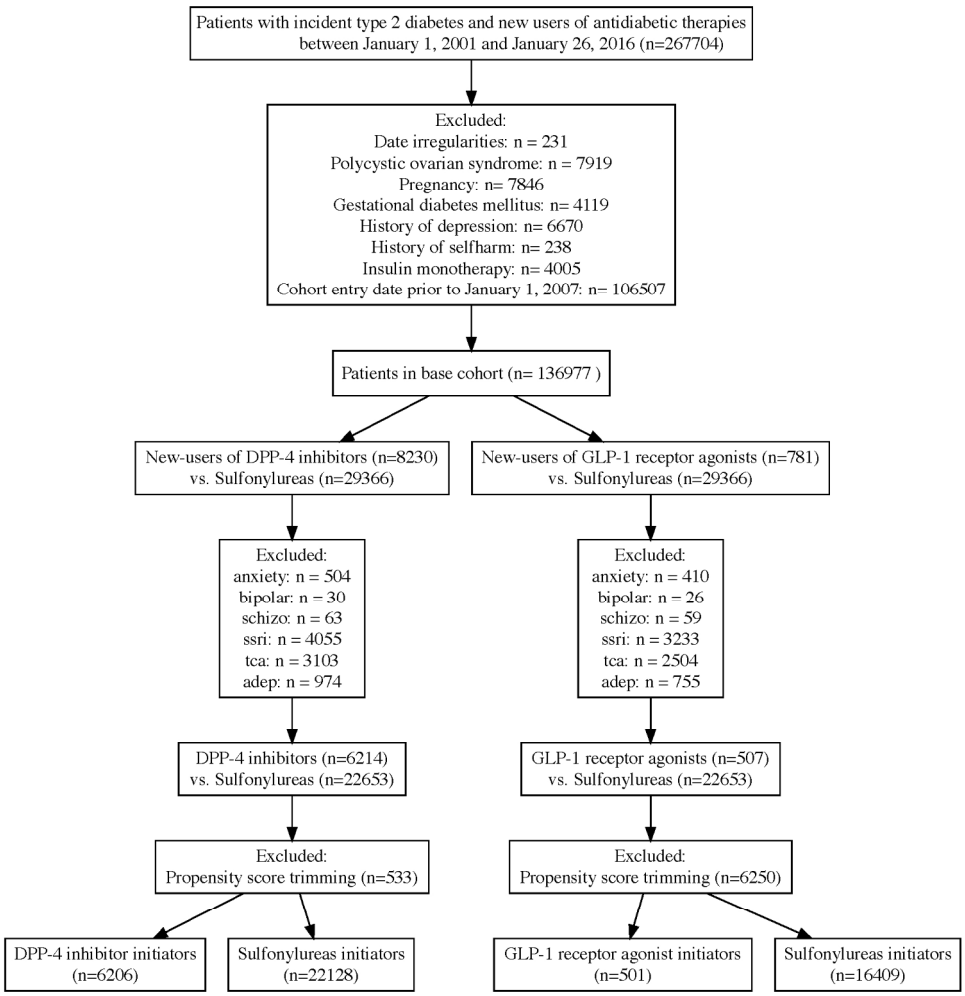
S = suppressed due to low number of events

FIGURES

Figure 1. Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

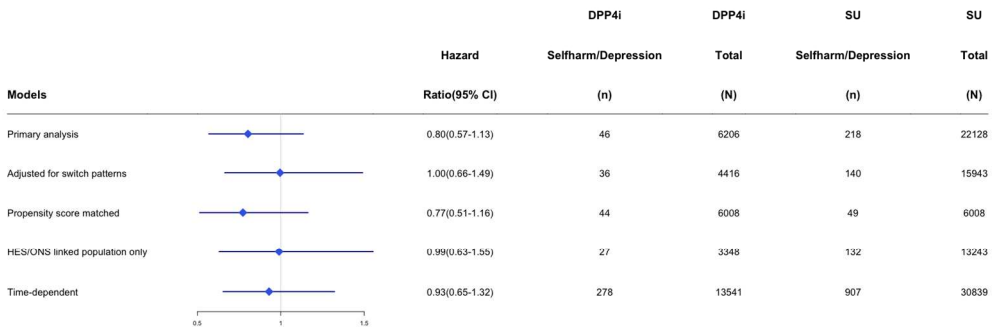
Figure 1. Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Figure 3. Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

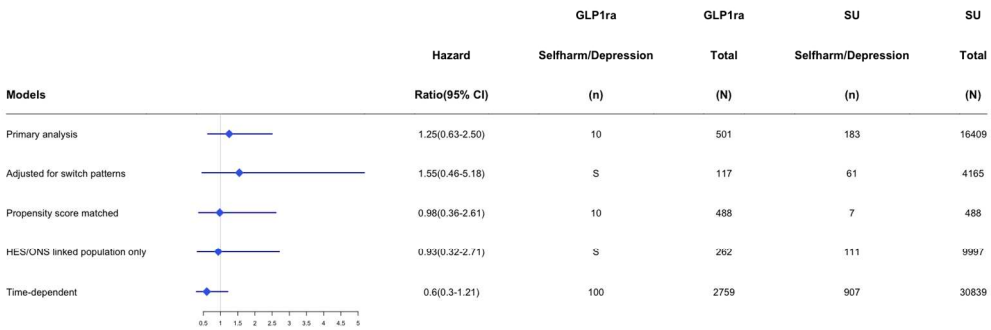


Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

177x181mm (300 x 300 DPI)



Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis



Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Supplementary Material

Appendix A: READ and ICD-10 Codes Used to Identify Depression

READ Code	Description
3004a	Depression
E2b..00	Depressive Disorder Nec
E204.00	Neurotic Depression Reactive Type
1b17.00	Depressed
Eu32z11	[X]Depression Nos
3004am	Mood Depressed
3004er	Reactive Depression
1b17.11	C/O - Feeling Depressed
3004l	Looking Depressed
E112.14	Endogenous Depression
E112.11	Agitated Depression
2960ad	Depression Agitated
E204.11	Postnatal Depression
E135.00	Agitated Depression
ICD-10 Code	Definition
F20.4	post-schizophrenic depression
F31.3	Bipolar affective disorder, current episode mild or moderate depression
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F32.0	Mild depressive episode
F32.1	Moderate depressive episode
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
F32.4	Depressive disorder, single episode in partial remission
F32.5	Depressive disorder, single episode in full remission
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified
F33.0	Recurrent depressive disorder, current episode

	mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified
F34.1	Dysthymia
F34.8	Other persistent mood [affective] disorders
F34.9	Persistent mood [affective] disorder, unspecified
F38.0	Other single mood [affective] disorders
F38.1	Other recurrent mood [affective] disorders
F38.8	Other specified mood [affective] disorders
F39	Unspecified mood [affective] disorder
F41.2	Mixed anxiety and depressive disorder
F99	Mental disorder, not elsewhere specified

Appendix B: READ and ICD-10 Codes Used to Identify Self-harm

READ Code	Description
SL..14	Overdose of biological substance
SL..15	Overdose of drug
SLHz.00	Drug and medicament poisoning not otherwise specified
TK..00	Suicide and self-inflicted injury
TK..11	Cause of overdose â€“ deliberate
TK..12	Injury â€“ self-inflicted
TK..13	Poisoning â€“ self-inflicted
TK..14	Suicide and self-harm
TK..15	Attempted suicide
TK..17	Para-suicide
TK0.00	Suicide + self-inflicted poisoning by solid/liquid substances
TK00.00	Suicide + self-inflicted poisoning by analgesic/antipyretic
TK01.00	Suicide + self-inflicted poisoning by barbiturates
TK01000	Suicide and self-inflicted injury by amylobarbitone
TK01100	Suicide and self-inflicted injury by barbitone
TK01400	Suicide and self-inflicted injury by phenobarbitone
TK02.00	Suicide + self-inflicted poisoning by other sedatives/hypnotics
TK03.00	Suicide + self-inflicted poisoning tranquillizer/psychotropic
TK04.00	Suicide + self-inflicted poisoning by other drugs/medicines

TK05.00	Suicide + self-inflicted poisoning by drug or medicine not otherwise specified
TK06.00	Suicide + self-inflicted poisoning by agricultural chemical
TK07.00	Suicide + self-inflicted poisoning by corrosive/caustic substance
TK0z.00	Suicide + self-inflicted poisoning by solid/liquid substance not otherwise specified
TK1.00	Suicide + self-inflicted poisoning by gases in domestic use
TK10.00	Suicide + self-inflicted poisoning by gas via pipeline
TK11.00	Suicide + self-inflicted poisoning by liquified petrol gas
TK1y.00	Suicide and self-inflicted poisoning by other utility gas
TK1z.00	Suicide + self-inflicted poisoning by domestic gases not otherwise specified
TK2.00	Suicide + self-inflicted poisoning by other gases and vapours
TK20.00	Suicide + self-inflicted poisoning by motor vehicle exhaust gas
TK21.00	Suicide and self-inflicted poisoning by other carbon monoxide
TK2z.00	Suicide + self-inflicted poisoning by gases and vapours not otherwise specified
TK3.00	Suicide + self-inflicted injury by hang/strangulate/suffocate
TK30.00	Suicide and self-inflicted injury by hanging
TK31.00	Suicide + self-inflicted injury by suffocation by plastic bag
TK3y.00	Suicide + self-inflicted injury by other means than hang/strangle/suffocate
TK3z.00	Suicide + self-inflicted injury by hang/strangle/suffocate not otherwise specified
TK4.00	Suicide and self-inflicted injury by drowning
TK5.00	Suicide and self-inflicted injury by firearms and explosives
TK51.00	Suicide and self-inflicted injury by shotgun
TK52.00	Suicide and self-inflicted injury by hunting rifle
TK54.00	Suicide and self-inflicted injury by other firearm
TK5z.00	Suicide and self-inflicted injury by firearms/explosives not otherwise specified
TK6.00	Suicide and self-inflicted injury by cutting and stabbing
TK60.00	Suicide and self-inflicted injury by cutting
TK60100	Self-inflicted lacerations to wrist
TK60111	Slashed wrists self-inflicted
TK61.00	Suicide and self-inflicted injury by stabbing
TK6z.00	Suicide and self-inflicted injury by cutting and stabbing not otherwise specified
TK7.00	Suicide and self-inflicted injury by jumping from high place
TK70.00	Suicide + self-inflicted injury â€“ jump from residential premises
TK71.00	Suicide + self-inflicted injury â€“ jump from other manmade structure
TK72.00	Suicide + self-inflicted injury â€“ jump from natural sites
TK7z.00	Suicide + self-inflicted injury â€“ jump from high place not otherwise specified
TKx.00	Suicide and self-inflicted injury by other means
TKx0.00	Suicide + self-inflicted injury â€“ jump/lie before moving object
TKx0000	Suicide + self-inflicted injury â€“ jumping before moving object
TKx1.00	Suicide and self-inflicted injury by burns or fire
TKx2.00	Suicide and self-inflicted injury by scald
TKx3.00	Suicide and self-inflicted injury by extremes of cold

TKx4.00	Suicide and self-inflicted injury by electrocution
TKx5.00	Suicide and self-inflicted injury by crashing motor vehicle
TKx6.00	Suicide and self-inflicted injury by crashing of aircraft
TKx7.00	Suicide and self-inflicted injury caustic substance
TKxy.00	Suicide and self-inflicted injury by other specified means
TKxz.00	Suicide and self-inflicted injury by other means not otherwise specified
TKy.00	Late effects of self-inflicted injury
TKz.00	Suicide and self-inflicted injury not otherwise specified
U2..00	[X]Intentional self-harm
U2..11	[X]Self-inflicted injury
U2..12	[X]Injury â€“ self-inflicted
U2..13	[X]Suicide
U2..14	[X]Attempted suicide
U2..15	[X]Para-suicide
U20.00	[X]Intentional self-poisoning/exposure to noxious substances
U20.11	[X]Deliberate drug overdose/other poisoning
U200.00	[X]Intentional self-poisoning/exposure to non-opioid analgesic
U200.11	[X]Overdose â€“ paracetamol
U200.12	[X]Overdose â€“ ibuprofen
U200.13	[X]Overdose â€“ aspirin
U200000	[X]Intentional self-poisoning/exposure to non-opioid analgesic at home
U200100	[X]Intentional self-poisoning non-opioid analgesic at residential institution
U200400	[X]Intentional self-poisoning non-opioid analgesic in street/highway
U200500	[X]Intentional self-poisoning non-opioid analgesic trade/service area
U200y00	[X]Intentional self-poisoning non-opioid analgesic other specified place
U200z00	[X]Intentional self-poisoning non-opioid analgesic unspecifified place
U201.00	[X]Intentional self-poisoning/exposure to antiepileptic
U201000	[X]Intentional self-poisoning/exposure to antiepileptic at home
U201z00	[X]Intentional self-poisoning antiepileptic unspecified place
U202.00	[X]Intentional self-poisoning/exposure to sedative hypnotic
U202.11	[X]Overdose â€“ sleeping tablets
U202.12	[X]Overdose â€“ diazepam
U202.13	[X]Overdose â€“ temazepam
U202.15	[X]Overdose â€“ nitrazepam
U202.16	[X]Overdose â€“ benzodiazepine
U202.17	[X]Overdose â€“ barbiturate
U202.18	[X]Overdose â€“ amobarbital
U202000	[X]Intentional self-poisoning /exposure to sedative hypnotic at home
U202400	[X]Intentional self-poisoning sedative hypnotic in street/highway
U202y00	[X]Intentional self-poisoning sedative hypnotic other specified place
U202z00	[X]Intentional self-poisoning sedative hypnotic unspecified place
U204.00	[X]Intentional self-poisoning/exposure to psychotropic drug
U204.11	[X]Overdose â€“ antidepressant

U204.12	[X]Overdose â€“ amitriptyline
U204.13	[X]Overdose â€“ SSRI
U204000	[X]Intentional self-poisoning /exposure to psychotropic drug at home
U204100	[X]Intentional self-poisoning psychotropic drug at residential institution
U204y00	[X]Intentional self-poisoning psychotropic drug other specified place
U204z00	[X]Intentional self-poisoning psychotropic drug unspecified place
U205000	[X]Intentional self-poisoning/exposure to narcotic drug at home
U205y00	[X]Intentional self-poisoning narcotic drug other specified place
U205z00	[X]Intentional self-poisoning narcotic drug unspecified place
U206.00	[X]Intentional self-poisoning/exposure to hallucinogen
U206400	[X]Intentional self-poisoning hallucinogen in street/highway
U207.00	[X]Intentional self-poisoning/exposure to other autonomic drug
U207000	[X]Intentional self-poisoning/exposure to other autonomic drug at home
U207z00	[X]Intentional self-poisoning other autonomic drug unspecified place
U208.00	[X]Intentional self-poisoning/exposure to other/unspecified drug/ medicament
U208400	[X]Intentional self-poisoning other/unspecified drug/medication in street/highway
U208y00	[X]Intentional self-poisoning other/unspecified drug/medication other specified place
U208z00	[X]Intentional self-poisoning other/unspecified drug/medication unspecified place
U20A.00	[X]Intentional self-poisoning organic solvent
U20A.11	[X]Self-poisoning from glue solvent
U20A000	"[X]Intentional self-poisoning organic solvent
U20A400	"[X]Intentional self-poisoning organic solvent
U20Az00	"[X]Intentional self-poisoning organic solvent
U20B.00	[X]Intentional self-poisoning/exposure to other gas/vapour U20B.11 [X]Self carbon monoxide poisoning
U20B000	[X]Intentional self-poisoning/exposure to other gas/vapour at home
U20B200	[X]Intentional self-poisoning other gas/vapour school/public admin area
U20By00	[X]Intentional self-poisoning other gas/vapour other specified place
U20Bz00	[X]Intentional self-poisoning other gas/vapour unspecified place
U20C.00	[X]Intentional self-poisoning/exposure to pesticide
U20C.11	[X]Self-poisoning with weedkiller
U20C.12	[X]Self-poisoning with paraquat
U20C000	[X]Intentional self-poisoning/exposure to pesticide at home
U20Cy00	[X]Intentional self-poisoning pesticide other specified place
U20y.00	[X]Intentional self-poisoning/exposure to unspecified chemical
U20y000	[X]Intentional self-poisoning/exposure to unspecified chemical at home
U20y200	[X]Intentional self-poisoning unspecified chemical school/public admin area
U20yz00	[X]Intentional self-poisoning unspecified chemical unspecified place
U21.00	[X]Intentional self-harm by hanging/strangulation/suffocation
U210.00	[X]Intentional self-harm by hanging/strangulation/suffocation at home

U211.00	[X]Intentional self-harm by hanging/strangulation/suffocation occurrence at residential institution
U21y.00	[X]Intentional self-harm by hanging/strangulation/suffocation other specified place
U21z.00	[X]Intentional self-harm by hanging/strangulation/suffocation unspecified place
U22.00	[X]Intentional self-harm by drowning and submersion
U221.0	[X]Intentional self-harm by drowning/submersion occurrence at residential institution
U22y.00	[X]Intentional self-harm by drowning/submersion occurrence at other specified place
U22z.00	[X]Intentional self-harm by drowning/submersion occurrence at unspecified place
U24.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge
U241.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge occurrence at residential institution
U242.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge in school/public admin area
U25.00	[X]Intentional self-harm by other/unspecified firearm discharge
U250.00	[X]Intentional self-harm other/unspecif firearm discharge occurrence at home
U26.00	[X]Intentional self-harm by explosive material
U27.00	[X]Intentional self-harm by smoke
U270.00	[X]Intentional self-harm by smoke fire/flames occurrence at home
U274.00	[X]Intentional self-harm by smoke fire/flame occurrence in street/highway
U27z.00	[X]Intentional self-harm by smoke fire/flames occurrence in unspecified place
U28.00	[X]Intentional self-harm by steam hot vapours/hot objects
U280.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence at home
U28z.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence in unspecified place
U29.00	[X]Intentional self-harm by sharp object
U290.00	[X]Intentional self-harm by sharp object occurrence at home
U291.00	[X]Intentional self-harm by sharp object occurrence at residential institution
U294.00	[X]Intentional self-harm by sharp object occurrence in street/highway
U29y.00	[X]Intentional self-harm by sharp object occurrence at other specified place
U29z.00	[X]Intentional self-harm by sharp object occurrence at unspecified place
U2A.00	[X]Intentional self-harm by blunt object
U2A0.00	[X]Intentional self-harm by blunt object occurrence at home
U2A1.00	[X]Intentional self-harm by blunt object occurrence at residential institution
U2A3.00	[X]Intentional self-harm by blunt object occurrence at sports/athletic area
U2B.00	[X]Intentional self-harm by jumping from a high place
U2B0.00	[X]Intentional self-harm by jumping from high place occurrence at home
U2B4.00	[X]Intentional self-harm by jumping from high place occurring in street/highway
U2B6.00	[X]Intentional self-harm by jumping from high place industrial/construction area

U2By.00	[X]Intentional self-harm by jumping from high place occurrence other specified place
U2Bz.0	0
U2C.00	[X]Intentional self-harm by jumping/lying before moving object
U2C1.00	[X]Intentional self-harm by jumping/lying before moving object occurrence at residential institution
U2C4.00	[X]Intentional self-harm by jumping/lying before moving object occurrence in street/highway
U2Cy.00	[X]Intentional self-harm by jumping/lying before moving object occurrence other specified place
U2D.00	[X]Intentional self-harm by crashing of motor vehicle
U2D0.00	[X]Intentional self-harm by crashing of motor vehicle occurrence at home
U2D4.00	[X]Intentional self-harm by crashing of motor vehicle occurrence in street/highway
U2D6.00	[X]Intentional self-harm by crashing of motor vehicle occurrence industrial/construction area
U2E.00 [X]Self-mutilation	
U2y.00	[X]Intentional self-harm by other specified means
U2y0.00	[X]Intentional self-harm by other specified means occurrence at home
U2y1.00	[X]Intentional self-harm by other specified means occurrence at residential institution
U2yz.00	[X]Intentional self-harm by other specif means occurrence at unspecified place
U2z.00	[X]Intentional self-harm by unspecified means
U2z0.00	[X]Intentional self-harm by unspecified means occurrence at home
U2z2.00	[X]Intentional self-harm by unspecified means occurrence school/institution/public administrative area
U2zy.00	[X]Intentional self-harm by unspecified means occurrence other specified place
U2zz.00	[X]Intentional self-harm by unspecified means occurrence at unspecified place
U30.11	[X]Deliberate drug poisoning
U41.00	[X]Hanging strangulation + suffocation undetermined intent
U44.00	[X]Rifle shotgun + larger firearm discharge undetermined intent
U45.00	[X]Other + unspecified firearm discharge undetermined intent
U4B.00	[X]Falling jumping/pushed from high place undetermine intent
U4Bz.00	[X]Fall jump/push from high place undetermine intent occurring at unspecified place
U72.00	[X]Sequelae of intentional self-harm assault + event of undetermined intent
U720.00	[X]Sequelae of intentional self-harm
ZRLfC12	Health of the Nation Outcome Scales item 2 â€“ nonaccidental self-injury
ZX..00	Self-harm
ZX..11	Self-damage
ZX1.00	Self-injurious behaviour
ZX1.12	SIB â€“ self-injurious behaviour
ZX1.13	Deliberate self-harm
ZX11.00	Biting self

ZX11.11	Bites self
ZX12.00	Burning self
ZX13.00	Cutting self
ZX13.11	Cuts self
ZX15.00	Drowning self
ZX18.00	Hanging self
ZX19.00	Hitting self
ZX19100	Punching self
ZX19200	Slapping self
ZX1B.00	Jumping from height
ZX1B100	Jumping from building
ZX1B200	Jumping from bridge
ZX1B300	Jumping from cliff
ZX1C.00	Nipping self
ZX1E.00	Pinching self
ZX1G.00	Scratches self
ZX1H.00	Self-asphyxiation
ZX1H100	Self-strangulation
ZX1H200	Self-suffocation
ZX1I.00	Self-scalding
ZX1J.00	Self-electrocution
ZX1K.00	Self-incineration
ZX1K.11	Setting fire to self
ZX1K.12	Setting self alight
ZX1L.00	Self-mutilation
ZX1L100	Self-mutilation of hands
ZX1L200	Self-mutilation of genitalia
ZX1L300	Self-mutilation of penis
ZX1L600	Self-mutilation of ears
ZX1LD00	[X]Self mutilation
ZX1M.00	Shooting self
ZX1N.00	Stabbing self
ZX1Q.00	Throwing self in front of train
ZX1Q.11	Jumping under train
ZX1R.00	Throwing self in front of vehicle
ZX1S.00	Throwing self onto floor
ICD-10code	Description
X60	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics

	[hallucinogens], not elsewhere classified
X63	Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X65	Intentional self-poisoning by and exposure to alcohol
X66	Intentional self-poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours
X67	Intentional self-poisoning by and exposure to other gases and vapours
X68	Intentional self-poisoning by and exposure to pesticides
X69	Intentional self-poisoning by and exposure to other and unspecified chemicals and noxious substances
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X73	Intentional self-harm by rifle, shotgun and larger firearm discharge
X74	Intentional self-harm by other and unspecified firearm discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X77	Intentional self-harm by steam, hot vapours and hot objects
X78	Intentional self-harm by sharp object
X79	Intentional self-harm by blunt object
X80	Intentional self-harm by jumping from a high place
X81	Intentional self-harm by jumping or lying before moving object
X82	Intentional self-harm by crashing of motor vehicle
X83	Intentional self-harm by other specified means
X84	Intentional self-harm by unspecified means
Y10	Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent
Y12	Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent
Y13	Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent
Y15	Poisoning by and exposure to alcohol, undetermined intent
Y16	Poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours, undetermined intent
Y17	Poisoning by and exposure to other gases and vapours, undetermined intent
Y18	Poisoning by and exposure to pesticides, undetermined intent
Y19	Poisoning by and exposure to other and unspecified chemicals and noxious substances, undetermined intent
Y20	Hanging, strangulation and suffocation, undetermined intent

Y21	Drowning and submersion, undetermined intent
Y22	Handgun discharge, undetermined intent
Y23	Rifle, shotgun and larger firearm discharge, undetermined intent
Y24	Other and unspecified firearm discharge, undetermined intent
Y25	Contact with explosive material, undetermined intent
Y26	Exposure to smoke, fire and flames, undetermined intent
Y27	Contact with steam, hot vapours and hot objects, undetermined intent
Y28	Contact with sharp object, undetermined intent
Y29	Contact with blunt object, undetermined intent
Y30	Falling, jumping or pushed from a high place, undetermined intent
Y31	Falling, lying or running before or into moving object, undetermined intent
Y32	Crashing of motor vehicle, undetermined intent
Y33	Other specified events, undetermined intent
Y34	Unspecified event, undetermined intent

Appendix C. Covariates Forced into the High Density Propensity Score

All covariates assessed in the 365 days prior to study index date
Age at index date
Alcohol Abuse [Never, Former, Current, Unknown]
BMI
Duration of treated diabetes [time between first oral antidiabetic drug and study index date]
History of: Cirrhosis Congestive heart failure Hypertension Hyperlipidemia Ischemic heart disease Peripheral heart disease
Number of hospitalizations
Most recent HbAlc value to index date
Number of distinct prescription drugs
Prior use of benzodiazepines or other hypnotics, antipsychotics, levothyroxine or triiodothyrinine, anticonvulsants, or mood stabilizers
Sex
Smoking status [Never, Former, Current, Unknown]
Socioeconomic status [quintiles of Index of Mulitiple Deprivation]
Use of other antidiabetic agents
Year of cohort entry

Appendix D. Measures of frequency and association for depression among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6207	22218		502	16728
Person-years follow-up	5591	18683		549	13628
Number of events	45	215		10	182
Incidence per 1000 person-years (95%CI)	8.0 (6.0-10.8)	11.5 (10.1-13.2)		18.2 (10-33.5)	13.4 (11.6-15.4)
Crude Hazard Ratio (95% CI)	0.70 (0.50-0.96)	-ref-		1.39 (0.74-2.63)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.57-1.14)	-ref-		1.22 (0.61-2.42)	-ref-

S = suppressed due to low number of events

Appendix E. Measures of frequency and association for self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6211	22180		502	16632
Person-years follow-up	5632	18839		563	13696
Number of events	S	5		S	S
Incidence per 1000 person-years (95%CI)	S	0.3 (0.1-0.6)		S	S
Crude Hazard Ratio (95% CI)	0.66 (0.08-5.69)	-ref-		S	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.07-8.21)	-ref-		S	-ref-

S = suppressed due to low number of events

Appendix F. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are matched 1:1 by propensity score.

	DPP4i	SU		GLP1ra	SU
Number of patients	6008	6008		488	488
Person-years follow-up	548	4488		529	349
Number of events	44	49		10	7
Incidence per 1000 person-years (95%CI)	8.0 (6-10.8)	10.9 (8.3-14.4)		18.9 (10.4-34.8)	20.1 (9.9-41.3)
Crude Hazard Ratio (95% CI)	0.75 (0.50-1.13)	-ref-		0.99 (0.37-2.61)	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.51-1.16)	-ref-		0.98 (0.36-2.61)	-ref-

Appendix G. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are adjusted for pattern of glucose-lowering therapy.

	DPP4i	SU		GLP1RA	SU
Number of patients	4416	15943		117	4165
Person-years follow-up	3743	12614		90	3327
Number of events	36	140		S	61
Incidence per 1000 person-years (95%CI)	9.6 (7-13.3)	11.1 (9.4-13.1)		33.4 (12.1-97.5)	18.3 (14.3-23.6)
Crude Hazard Ratio (95% CI)	0.86 (0.60-1.24)	-ref-		1.82 (0.57-5.80)	-ref-
Adjusted Hazard Ratio (95% CI)	1.00 (0.66-1.49)	-ref-		1.55 (0.46-5.18)	-ref-

S = suppressed due to low number of events

Appendix H. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to only those with HES/ONS linked data.

	DPP4i	SU		GLP1ra	SU
Number of patients	3348	13243		262	9997
Person-years follow-up	2841	10762		290	7904
Number of events	27	132		S	111
Incidence per 1000 person-years (95%CI)	9.5 (6.5-13.8)	12.3 (10.3-14.5)		13.8 (5.6-35.3)	14 (11.7-16.9)
Crude Hazard Ratio (95% CI)	0.78 (0.51-1.17)	-ref-		1.00 (0.37-2.72)	-ref-
Adjusted Hazard Ratio (95% CI)	0.99(0.63-1.55)	-ref-		0.93 (0.32-2.71)	-ref-

Appendix I. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to second-line therapy after metformin monotherapy.

	DPP4i	SU		GLP1ra	SU
Number of patients	1255	4612		65	2112
Person-years follow-up	1191	3601		47	1680
Number of events	11	48		S	29
Incidence per 1000 person-years (95%CI)	9.2 (5.2-16.5)	13.3 (10.1-17.7)		43(13.3-155.3)	17.3 (12-24.8)
Crude Hazard Ratio (95% CI)	0.71 (0.37-1.38)	-ref-		2.49(0.59-10.45)	-ref-
Adjusted Hazard Ratio (95% CI)	0.67 (0.34-1.34)	-ref-		1.92(0.44-8.31)	-ref-

S = suppressed due to low number of events

Appendix J. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when BMI categories (in addition to hdps deciles) were added to the Cox proportional regression model.

	DPP4i	SU		GLP1ra	SU
Number of patients	6206	22128		501	16409
Person-years follow-up	5589	18596		549	13418
Number of events	46	218		10	183
Incidence per 1000 person-years (95%CI)	8.2 (6.2-11)	11.7 (10.3-13.4)		18.2 (10-33.5)	13.6 (11.8-15.8)
Crude Hazard Ratio (95% CI)	0.70 (0.51-0.96)	-ref-		1.36 (0.72-2.58)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.58-1.15)	-ref-		1.25 (0.63-2.51)	-ref-

S = suppressed due to low number of events

Appendix K. Time-dependent Cox regression for DPP-4 inhibitor monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
DPP-4i monotherapy	-0.07	0.93	0.65	1.32	0.18	0.69
DPP-4i/SU	-0.53	0.59	0.34	1.02	0.28	0.06
DPP-4i/Other	-0.16	0.85	0.70	1.04	0.10	0.11
DPP-4i/SU/Other	-0.13	0.88	0.68	1.14	0.13	0.33

*Adjusted for deciles of hdps

Appendix L. Time-dependent Cox regression for GLP-1 receptor agonist (GLP1ra) monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
GLP1ra monotherapy	-0.51	0.60	0.30	1.21	0.36	0.15
GLP1ra /SU	0.45	1.57	0.78	3.18	0.36	0.21
GLP1ra /Other	0.14	1.16	0.88	1.52	0.14	0.31
GLP1ra /SU/Other	-0.31	0.73	0.47	1.15	0.23	0.18

*Adjusted for deciles of hdps

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Cohort in title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Structured abstract provided**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Introduction – paragraphs 1 and 2**
Objectives	3	State specific objectives, including any prespecified hypotheses **Introduction – paragraph 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Methods, Study Design and Data Sources section, paragraph 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods, Study Design and Data Sources section, paragraph 1**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Methods, Study Cohort section, paragraph 1**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Methods, Exposure and Outcome Definitions section**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Methods, Exposure and Outcome Definitions section** **Supplemental appendix**
Bias	9	Describe any efforts to address potential sources of bias **Methods, Statistical Analysis section, paragraphs 2 and 3**
Study size	10	Explain how the study size was arrived at **Figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Methods, Exposure and Outcome Definitions section** **Methods, Statistical Analysis section**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Methods, Statistical Analysis section**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) **Table 3** **Results section**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Table 3** **Results section** **Supplemental appendix**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Results section** **Table 3**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Results section, paragraph 5** **Figure 2** **Figure 3** **Supplemental appendix**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Discussion section, paragraph 1**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Discussion section, paragraph 5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Discussion section, final paragraph**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding support**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Examining the Risk of Depression or Self-Harm Associated with Incretin-based Therapies Used to Manage Hyperglycemia in Patients with Type 2 Diabetes: A Cohort Study Using the UK Clinical Practice Research Datalink

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023830.R2
Article Type:	Research
Date Submitted by the Author:	27-Aug-2018
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Pharmacology and therapeutics, Epidemiology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Depression & mood disorders < PSYCHIATRY, cohort study, pharmacoepidemiology

Examining the Risk of Depression or Self-Harm Associated with Incretin-based Therapies Used to Manage Hyperglycemia in Patients with Type 2 Diabetes: A Cohort Study Using the UK Clinical Practice Research Datalink

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Abbreviated Title: Depression and Self-Harm Among Incretin-based Therapy Users

Key terms: cohort study, type 2 diabetes, dipeptidyl-peptidase 4 inhibitors, glucagon-like receptor 1 agonists, depression, suicide, self-harm

Counts: Abstract=290; Manuscript= 3079; Figures=3; Tables=3; References=45

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Abstract

Objectives: To compare population-based incidence rates of new-onset depression or self-harm in patients initiating incretin-based therapies with that of sulfonylureas (SU) and other glucose-lowering agents.

Design: Population-based cohort study

Setting: Patients attending primary care practices registered with the UK-based Clinical Practice Research Datalink (CPRD).

Participants: Using the UK-based Clinical Practice Research Datalink (CPRD), we identified two incretin-based therapies cohorts: (1) DPP-4i-cohort, consisting of new-users of DPP-4 inhibitors and sulfonylureas, and (2) GLP-1RA-cohort, consisting of new-users of GLP-1 receptor agonists and sulfonylureas, between Jan-2007 and Jan-2016. Patients with a prior history of depression, self-harm, and other serious psychiatric conditions were excluded.

Main outcome measures: The primary study outcome comprised a composite of new-onset depression or self-harm. Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Deciles of high-dimensional propensity scores and concurrent number of glucose-lowering agents were used to adjust for potential confounding.

Results: We identified new-users of 6206 DPP-4i and 22128 sulfonylureas in the DPP-4i-cohort, and 501 GLP-1RA and 16409 sulfonylurea new-users in the GLP-1RA-cohort. The incidence of depression or self-harm was 8.2 vs. 11.7 events/1000-person-years in the DPP-4i-cohort and 18.2 vs. 13.6 events/1000-person-years in the GLP-1RA-cohort for incretin-based therapies vs sulfonylureas, respectively. Incretin-based therapies were not associated with an increased or decreased incidence of depression or self-harm compared to sulfonylureas (DPP-4i-cohort: unadjusted hazard ratio (HR) 0.70, 95% confidence internal (CI): 0.51-0.96) adjusted HR 0.80, 95% CI: 0.57-1.13; GLP-1RA-cohort: unadjusted hazard ratio (HR) 1.36, 95% confidence internal (CI): 0.72-2.58; adjusted HR 1.25, 95% CI: 0.63-2.50). Consistent results were observed for other glucose-lowering comparators including insulin and thiazolidinediones.

Conclusions: Our findings suggest that the two incretin-based therapies are not associated with an increased or decreased risk of depression or self-harm.

Strengths and limitations of the study

- This study used a new-user active comparator design with high dimensional propensity scores to control for confounding
- Depression is likely underestimated using diagnostic codes, although previous studies have shown positive predictive values around 90% or greater
- There were a limited number of self-harm events and the study was not powered to detect clinically relevant differences across exposure groups for this component of the composite outcome
- This study cannot rule out small or modest difference in risk of depression or self-harm between incretin-based therapy users and other glucose-lowering due to study power limitations

Introduction

Patients with diabetes frequently have coexisting depression with a prevalence ranging from 12% to 27%.[1] Depression is not only associated with diabetes but with an increased risk of diabetes-related complications,[2] decreased quality of life,[3] and decreased life-expectancy.[4] Diabetes is also associated with new-onset depression; however, the temporal association between diabetes and depression remains unclear.[5,6] Moreover, diabetes is associated with an increased risk of intentional self-harm,[7,8] albeit there is significant heterogeneity between studies assessing the association between diabetes and suicide.[9] It has been postulated that certain glucose-lowering pharmacotherapies may have a positive influence on the symptoms of depression, although the evidence is sparse.[10–15] The incretin-based therapies in particular may have neuropsychiatric effects given the presence of glucagon-like peptide-1 (GLP-1) receptors in the central nervous system.[16,17]

Concerns surrounding central nervous system effects stem from a case report of exenatide-induced depression and from pooled adverse event data from pre-marketing clinical trials for sitagliptin.[18–20] Pooled event rates for the latter suggested a 4-fold increased risk of suicide ideation and completed suicide in sitagliptin users compared to non-users.[19,21] Animal models suggest adverse neuropsychiatric effects are biologically plausible given the expression of GLP-1 receptors in the brain.[20] Furthermore, studies have shown low dipeptidyl peptidase-4 (DPP-4) activity is correlated with depression.[22–24] Although the case-report mentioned above suggested a potential increased risk of

depression, a recent study reported positive effects of GLP-1 receptor agonists on patients well-being.[25] Therefore alternations in DPP-4 enzymatic activity may modulate the pathophysiology of neuropsychiatric conditions such as major depression.

Using data from a population-based cohort of patients with type 2 diabetes, we aimed to quantify the association between incretin-based therapies and the composite of new-onset depression and self-harm.

Methods

Study Design and Data Sources

We conducted a population-based cohort study using data from the Clinical Practice Research Datalink (CPRD), which captures electronic medical information for primary care encounters by general practitioners in the United Kingdom (UK).[26] The CPRD contains de-identified individual-level longitudinal data collected from a subset of primary care practices (~700) in the UK. The CPRD data is a representative sample that is similar to the overall UK population in age, sex, and ethnicity.[27] The database includes sociodemographic and lifestyle variables (e.g., alcohol consumption), physiological measures (e.g., blood pressure), laboratory testing (e.g., glycated hemoglobin [A1c]), physician-assigned diagnoses using the Read classification system, and prescription records from general practitioner records. Data quality checks are performed in accordance with standardized guidelines that certify practices as up-to-standard. Furthermore, over 350 validation studies have been performed using the CPRD.[28,29] Information on hospitalizations and causes of death are available for a subset of CPRD patients through linkages with the external databases. Details regarding the data quality, linkages, and utility are available elsewhere.[30] The CPRD has been used extensively to study associations between drugs and depression and self-harm.[31–35] Our study protocol was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA, August 2017) and received approval from the Health Research Ethics Board at Memorial University.

Study Cohorts

Our source population consisted of all patients over 18 years of age with a minimum of 12-months of up-to-standard medical history in the CPRD database that received a new diagnosis for type 2 diabetes or a new prescription for any glucose-lowering therapy between January 1, 2001 and the February 2016 CPRD dataset build. We used a 365-day washout period to define a new diagnosis or new glucose-lowering therapy use. A sub-cohort of patients (~58%) selected from the source population was linked to Hospital Episode Statistics (HES – follow-up until 31March2014), Office of National Statistics (ONS – follow-up until 30April2014), and index of multiple deprivation (IMD [2010]) data to capture hospital records, causes of death, and socioeconomic status information, respectively. Women with polycystic ovarian syndrome, gestational diabetes, or whom were pregnant during the study period were

excluded. In addition, we excluded patients with a study entry date prior to January 1, 2007 as the first incretin-based therapies became available in the UK in early 2007.

We identified two main study cohorts. Specifically, the first cohort consisted of new-users of DPP-4 inhibitors and new-users of sulfonylureas (DPP-4 inhibitor cohort) and the second cohort consisted of new-users of GLP-1 receptor agonists and new-users of sulfonylureas (GLP-1 receptor agonist cohort). Although new-users of sulfonylureas served as the reference population for both cohorts, these individuals were selected separately for each cohort as prior use of other non-incretin glucose-lowering agents was permitted. To minimize potential selection bias within the above cohorts, we excluded patients with a history of depression, self-harm, anxiety, and other serious psychiatric conditions in the year prior to a patient's cohort entry date.

Exposure and Outcome Definitions

Within each incretin-based therapy cohort, we defined person-time exposure to all classes of glucose-lowering therapy including (1) DPP-4 inhibitors, (2) GLP-1 receptor agonists, (3) Sulfonylureas, (4) Metformin, (5) Thiazolidinediones, (6) Sodium glucose co-transporter-2 inhibitors, (7) Meglitinides, (8) Acarbose, (9) Insulin, and (10) no glucose-lowering drug therapy (i.e. diet/lifestyle). Patient's contributed person-time to each of the aforementioned categories on the day of their first prescription or date of diagnosis (defined as the patient's index date) until a patient discontinued the drug, left a CPRD practice, died, or on the final date of follow-up, whichever occurred first. To account for potential non-adherence, we included a portion of follow-up time following the end of the expected medication supply that was equivalent to 50% of the prescription duration as a period of exposure.

Our primary outcome the composite of either new-onset depression or self-harm, including suicide and suicidal ideation. If a patient experienced more than one event, the date of the first event was used. New-onset depression or episodes of self-harm were identified using diagnostic codes from either the CPRD, HES, or ONS data sources (specific codes available in supplemental material in Appendices A and B).

Statistical Analysis

Unadjusted and adjusted Cox proportional hazards regression was used to quantify the association between incretin-based therapies and depression or self-harm. Our primary exposure contrasts of interest were DPP-4 inhibitors vs. sulfonylureas and GLP-1 receptor agonists vs. sulfonylureas within the DPP-4 inhibitor and GLP-1 receptor agonists cohorts respectively. Sulfonylureas were chosen a priori as the main reference group given their use in clinical practice as second or third agents resembles incretin-based therapies. Patients contributed follow-up time from the initiation of the incretin-based therapy of interest or comparator until they experienced the composite outcome of interest or were censored. Censoring occurred upon the earliest date of the following events: discontinuation of the incretin-based therapy of interest or comparator, switching between an incretin-based therapy to the comparator (or vice-versa), leaving a CPRD practice site, death, end of study period.

To adjust for potential confounders, we used a high-dimensional propensity score (hdPS) algorithm to select up to 40 empirical covariates.[36] Using a multivariable logistic regression model that included the both empirically derived and predefined (age, sex, alcohol abuse, body mass index, duration of treated diabetes, comorbidities, number of hospitalizations, HbA1c, prior medications use, smoking status, socioeconomic status [quintiles of the index of multiple deprivation], use of other glucose-lowering therapies, year of cohort entry. A detailed list of covariates forced into propensity score model is shown in Appendix C) covariates, we calculated the probability of initiating a DPP-4 inhibitor versus a sulfonylurea (or comparator for sensitivity analysis). Patients with overlapping propensity scores were included in the analysis. A separate hdPS procedure was run for the GLP-1 receptor agonist cohort. Adjusted hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards regression model with deciles of the hdPS and variable indicating the number of glucose-lowering agents during follow-up (1, 2, 3 or more). We used standard graphical approaches to assess model assumptions for which no violations were noted.

Secondary analyses included alternative comparator groups and components of composite outcome (i.e., depression and self-harm as separate outcomes). In addition, we conducted several additional sensitivity analyses. First, we used two alternative methods to adjust for potential confounding including a matched propensity score approach (1:1 -

matching using greedy nearest neighbor approach with a caliper set at 0.2 times the standard deviation of the natural logarithm of the propensity score) and grouping patients with identical patterns of glucose-lowering therapies prior to and following cohort initiation. For the latter approach, an example of how we grouped patients is as follows. Patients who started with metformin monotherapy and added an incretin-based therapy would be grouped with patients who also started metformin monotherapy and then added the comparator drug of interest. Groups with less than 25 patients were excluded from this analysis. We used a categorical variable to adjust for all groups within our multivariable Cox proportional hazards model. Second, we ran several analyses using restricted cohorts including restricting our cohort to patients eligible for HES/ONS linkage (i.e., patients with hospital and death certificate records), restricting to monotherapy users, restricting to a cohort of metformin monotherapy users who added the incretin-based therapy of interest or a sulfonylurea. Third, we added BMI (as a categorical variable) to Cox proportional hazards model given that weight may be a confounding factor.[37,38] Fourth, we used time-dependent variables to classify our exposures of interest throughout follow-up time. All analyses were conducted with R version 3.3.3.

Patient and Public Involvement

No patients were involved in any aspect of the study.

Results

DPP-4 Inhibitor Cohort

Within the DPP-4 inhibitor new user cohort, there were 6206 initiators of a DPP-4 inhibitor and 22128 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 324 (362) days for DPP-4 inhibitor users and 299 (385) days for sulfonylurea users. Compared to sulfonylurea users, DPP-4 inhibitor users were on average younger, had fewer hospitalizations in the year prior to cohort entry, and less likely to have impaired kidney function. Patient characteristics were well-balanced following propensity score matching (Table 1). There were a total 264 patients identified with new-onset depression or self-harm.

The incidence of depression or self-harm was 8.2 per 1000 person-years in DPP-4 inhibitor users compared to 11.7 per 1000 person-years in sulfonylurea users (unadjusted

hazard ratio (HR): 0.70 95% confidence interval (CI) 0.51-0.96 [table 2]). Similarly, the crude incidence rates were smaller for DPP-4 inhibitor users versus other comparators (10.0 vs. 10.8 per 1000 person-years for TZDs; 9.8 vs. 20.7 for insulin users). However, following adjustment for potential confounding variables, there was no significant association between DPP-4 inhibitor use and the risk of depression or self-harm for all comparator groups (sulfonylurea comparator: adjusted HR 0.80, 95% CI 0.57-1.13; TZD comparator: adjusted HR 1.17, 95% CI 0.70-1.96; insulin comparator: adjusted HR 0.98, 95% CI 0.53-1.83). Appendices D and E show the results for the risks of depression and self-harm separately.

GLP-1 Receptor Agonist Cohort

Within the GLP-1 receptor agonist cohort, there were 501 initiators of a GLP-1 receptor agonist and 16409 initiators of a sulfonylurea (Figure 1). The mean (standard deviation) follow-up time was 397 (409) days for GLP-1 receptor agonist users and 292 (373) days for sulfonylurea users. Compared to sulfonylurea users, GLP-1 receptor agonist users were on average younger, more likely female, used more drugs in the year prior to cohort entry, had a lower baseline HbA1c, more likely to have used several medications prior to cohort entry including insulin, SSRIs, or other antidepressant. Following propensity score matching, baseline patient characteristics were well-balanced (Table 3). There were a total 193 patients identified with new-onset depression or self-harm.

The incidence rate of depression or self-harm was non-significantly higher for GLP-1 receptor users compared to sulfonylurea users (18.2 vs. 13.6 per 1000 person-years; unadjusted HR 1.36, 95% CI 0.72-2.58; adjusted HR 1.25, 95% CI 0.63-2.50), TZDs (16.4 vs. 12.5 per 1000 person-years; unadjusted HR 1.32, 95% CI 0.72-2.42; adjusted HR 1.18. 95% CI 0.53-2.65), and insulin users (13.6 vs. 20.7 per 1000 person-years; unadjusted HR 0.74, 95% CI 0.35-1.56; adjusted HR 1.07, 95% CI 0.39-2.94). All measured associations remained non-significant following adjustment for potential confounders (Table 2). Appendix D shows the results for depression analyzed as a separate outcome. We were unable to analyze results for self-harm separately, due to small numbers of events (Appendix E).

Sensitivity Analyses

Figures 2 and 3 provide the number of events per treatment exposure group and measures of association for selected sensitivity analyses across the main DPP-4 inhibitor and

GLP-1 receptor agonist cohorts. There were too few events to run a stable statistical model for all pre-specified sensitivity analyses (e.g. new monotherapy users); however, findings from models that were run were consistent with our main results suggesting that DPP-4 inhibitor use did not have an increased or decreased risk of new-onset depression (Appendix F to L).

Discussion

New users of DPP-4 inhibitors and new users of GLP-1 receptor agonists did not have an increased or decreased risk of a new diagnosis of depression or episode of self-harm. These findings extend our current knowledge regarding the relative safety of the incretin-based therapies used to manage hyperglycemia in patients with type 2 diabetes.

The impetus for our study was the safety signal generated by randomized controlled trials and a case-report suggesting that incretin-based therapies may affect the risk of depression or self-harm. Specifically, early trial data found a 4-times greater risk of suicidal ideation or completed suicide in sitagliptin users vs glipizide users.[19,21] A higher incidence of depression was also observed in the long-term safety population among phase-3 clinical trial in sitagliptin 100mg users (13/429) compared to placebo (0/154); however, the incidence of psychiatric events was no different among pooled phase 3 studies (3.0% in sitagliptin 100mg users; 2.4% in sitagliptin 200mg users, and 3.2% in placebo users).[20] Moreover, a case-report has also been published regarding exenatide-induced depression.[18]

Despite our findings suggesting a lack of association between incretin-based agents and depression or self-harm, there is a substantial evidence-base from animal models that suggest incretin-based therapies may affect mood disorders. Anderberg and colleagues found differential effects of acute versus chronic exposure to a GLP-1 receptor agonist.[39] Acute activation of GLP-1 receptors was associated with anxiogenic effects, whereas chronic GLP-1 receptor activation did not elicit anxiogenic effects in Sprague-Dawley rats. In fact, chronic exposure to a GLP-1 receptor agonist was associated with a decrease in depressive-like behavior. Furthermore, acute stimulation of GLP-1 receptors affected serotonin turnover and serotonin receptor expression in the amygdala; however, chronic stimulation did not affect serotonin turnover or receptor expression. In addition to effects on serotonin, activation of GLP-1 may have mood effects through impacting central dopamine levels.[40] A mice model suggests that liraglutide, a GLP-1 receptor agonist, has antipsychotic properties possibly

through its affecting dopamine activity in the brain.[41] Interestingly, the DPP-4 inhibitor sitagliptin, did not exhibit the same antipsychotic properties.

Another possible mechanism by which glucose lowering therapies may affect mood disorders is through the reduction in inflammatory cytokines/mediators. Moulton et al reported improvement in depressive symptoms over 1-year in a cohort of 1735 newly diagnosed patients with type 2 diabetes.[10] The improvement in depressive symptoms measure by the PHQ-9 was independent of change in glycemic control and was correlated with a change in the inflammatory marker hs-CRP. Furthermore, a meta-analysis found that pioglitazone was associated with a reduction in symptoms of depression compared to placebo (pooled odds ratio = 3.3, 95% confidence interval 1.4 to 7.8).[11] A 12-week open-label study also found that pioglitazone was associated with a reduction in depression symptoms as well as a decrease in c-reactive protein and decreased insulin resistance.[12] Indeed, a population-based cross-sectional study found that numerous inflammatory markers (e.g., c-reactive protein, inerleukin-1 receptor agonist, monocyte chemotactic protein-1, white blood cell count, triglyceride) were associated with depression in patients with type 2 diabetes.[42] To further test this hypothesis among DPP-4 inhibitor users, there is an ongoing small clinical trial evaluating the effect of sitagliptin on symptoms of depression in the elderly (EudraCT Number: 2015-004527-32).[43]

Our study is subject to the standard limitations of observational cohort studies including the potential for residual and unmeasured confounding. Although we adjusted for over 70 potential confounders using an HdPS approach, we were not able to capture all relevant potential confounders such as severity of depressive symptoms and patient level socioeconomic status. Our follow-up time was also limited (DPP-4 cohort mean follow-up time = 305 days; GLP-1 receptor agonist cohort mean follow-up = 296 days), therefore, it is possible that a longer time frame was required to detect an association. However, it would be expected that an effect on depression symptoms mediated by serotonin or dopaminergic central pathways would be apparent after 4 to 6 weeks or sooner. There were a limited number of self-harm events and our study was not powered to detect clinically relevant differences across exposure groups for this component of our composite outcome. Similarly, given the lower and upper limits of the 95% confidence intervals, our study cannot rule out small or moderate differences in the risk of depression across exposure groups. Misclassification of the exposure or outcome variables of interest may have also impacted our

findings. Our exposure variables of interest (incretin-based therapies) were measured based on primary care prescription records and therefore may overestimate true exposure due to primary and secondary non-adherence. In addition, prescriptions written by specialists are not captured in the CPRD. It is possible that when the incretin-based therapies were introduced they were more frequently prescribed by specialists and our study would miss the initial prescription, however, subsequent prescriptions written by general practitioners would be captured. Previous studies have shown that depression is likely underestimated using diagnostic codes, although positive predictive values have generally been greater than 90% using ICD-10 codes.[44] Under-ascertainment of depression would likely be non-differential between our exposure groups of interest and therefore bias our findings toward the null. Suicide and self-harm have also been shown to be underestimated using CPRD data and the use of linked mortality data via the Office of National Statistics improves the sensitivity for capturing suicide and self-harm; however, underreporting of events is still expected.[45] In addition, the role of incretin-based agents may have shifted over time whereby when they were first introduced to the market were not used commonly as 2nd line agents and sulfonylureas may have been used as first or second-line agents. We attempted to control for both temporal trends and timing of therapy by using calendar time, duration of and prior exposure of glucose-lowering therapies as covariates in the propensity score.

Our findings provide some reassurance regarding the safety of the incretin-based therapies in the treatment of type 2 diabetes. Specifically, our study results suggest that there is not a clinically relevant association between either DPP-4 inhibitors or GLP-1 receptor agonists and depression or self-harm.

Authors' Contributions: JMG, EC, WKM, LKT and SRM, were involved in the concept and design of the study. JMG was responsible for drafting the first version of the manuscript. All authors contributed to the interpretation of data. JMG, EC, WKM, and LKT provided revisions to the manuscript. JMG will act as guarantor for the study.

Acknowledgements: JMG is supported as a New Investigator Award from the Canadian Institute of Health Research and a Clinician Scientist Award from Diabetes Canada. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the author/s alone.

Funding Support: This work was supported by an operating grant from the Canadian Institute for Health Research (FRN173599 – 287647).

Competing Interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work; no financial relationships that may be relevant to the submitted work; and no other relationships or activities that could appear to have influence the submitted work.

Ethical approval: This study was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA) and received approval from the Health Research Ethics Board at Memorial University.

located; and, vi) licence any third party to do any or all of the above.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data Sharing: no additional data available.

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TABLES

Table 1. Patient Characteristics of New-user DPP-4 Inhibitor Cohort Before and After Propensity Score Matching. and GLP-1 Receptor Agonist Cohorts.

	DPP4 Inhibitor New User Cohort Before Propensity Score Matching		DPP4 Inhibitor New User Cohort After Propensity Score Matching	
	DPP-4i (n=6206)	SU (n=22128)	DPP-4i (n=6008)	SU (n=6008)
Age in yrs (sd)	58(12.2)	60.5(13.8)	58.1(12.2)	58.2(12.5)
Female	2258(36.4%)	8107(36.6%)	2189(36.4%)	2187(36.4%)
Measure of deprivation				
Least	624(10.1%)	2492(11.3%)	603(10%)	594(9.9%)
Most	615(9.9%)	2342(10.6%)	603(10%)	614(10.2%)
Unknown	2862(46.1%)	8780(39.7%)	2739(45.6%)	2683(44.7%)
Diabetes duration in yrs (sd)	2.0(1.8)	1.0(1.5)	1.9(1.7)	1.9(1.8)
Body Mass Index >30	4162(67.1%)	10661(48.2%)	3994(66.5%)	3978(66.2%)
Number of hospitalizations in year prior to cohort entry				
0	5647(91%)	18516(83.7%)	5452(90.7%)	5470(91%)
1	378(6.1%)	2105(9.5%)	375(6.2%)	379(6.3%)
2	109(1.8%)	784(3.5%)	109(1.8%)	92(1.5%)
3+	72(1.2%)	723(3.3%)	72(1.2%)	67(1.1%)
Number of drugs in year prior to cohort entry				
0-4	721(11.6%)	3098(14%)	703(11.7%)	671(11.2%)
5-10	3204(51.6%)	10379(46.9%)	3081(51.3%)	3119(51.9%)
11+	2281(36.8%)	8651(39.1%)	2224(37%)	2218(36.9%)
HbA1c				
<6.5%	242(3.9%)	1393(6.3%)	238(4%)	233(3.9%)
6.5-7.5%	1104(17.8%)	3349(15.1%)	1049(17.5%)	1053(17.5%)
7.5-9%	2831(45.6%)	7121(32.2%)	2701(45%)	2694(44.8%)
9%+	2000(32.2%)	9833(44.4%)	1991(33.1%)	2007(33.4%)
Unknown	29(<1%)	432(2%)	29(<1%)	21(<1%)
e*GFR* <60	883(14.2%)	4429(20%)	857(14.3%)	890(14.8%)
Diagnoses in year prior to cohort entry				
Heart Failure	68(1.1%)	369(1.7%)	68(1.1%)	51(<1%)
Hypertension	1095(17.6%)	4475(20.2%)	1066(17.7%)	1087(18.1%)
Dyslipidemia	213(3.4%)	1093(4.9%)	213(3.5%)	212(3.5%)
Ischemic heart	174(2.8%)	1033(4.7%)	171(2.8%)	168(2.8%)
Peripheral vascular	25(<1%)	145(<1%)	25(<1%)	24(<1%)
Prescription drug use in year prior to cohort entry				
Metformin	5775(93.1%)	16534(74.7%)	5578(92.8%)	5638(93.8%)
Acarbose	S	8(<1%)	S	S
SGLT2 inhibitors	38(<1%)	93(<1%)	38(<1%)	40(<1%)
Meglitinide	47(<1%)	39(<1%)	38(<1%)	29(<1%)
Thiazolidinedione	252(4.1%)	403(1.8%)	222(3.7%)	209(3.5%)
Insulin	82(1.3%)	331(1.5%)	80(1.3%)	86(1.4%)
Hypnotic	332(5.3%)	1486(6.7%)	328(5.5%)	324(5.4%)
Mood	85(1.4%)	280(1.3%)	81(1.3%)	83(1.4%)
Anticonvulsant	271(4.4%)	832(3.8%)	260(4.3%)	266(4.4%)
Antipsychotics	176(2.8%)	829(3.7%)	172(2.9%)	171(2.8%)

S = suppressed due to low number of events

Table 2. Measures of frequency and association for depression or self-harm in new-users of DPP-4 Inhibitors (DPP4i) or new-users of GLP-1 receptor agonists (GLP1ra) vs. sulfonylureas (SU), thiazolidinediones (TZD), or insulin.

	DPP4 Inhibitor New User Cohort		GLP1 Receptor Agonist New User Cohort	
COMPARATOR: SU				
	DPP4i	**SU**	**GLP1ra**	**SU**
Number of patients	6206	22128	501	16409
Person-years of follow-up	5589	18596	549	13418
Number of Events	46	218	10	183
Incidence per 1000 person-years (95%CI)	8.2(6.2-11)	11.7(10.3-13.4)	18.2(10-33.5)	13.6(11.8-15.8)
Crude HR	0.70(0.51-0.96)	-ref-	1.36(0.72-2.58)	-ref-
Adjusted HR	0.80(0.57-1.13)	-ref-	1.25(0.63-2.50)	-ref-
COMPARATOR: TZD				
	DPP4i	**TZD**	**GLP1ra**	**TZD**
Number of patients	9565	2512	851	2011
Person-years of follow-up	9190	2786	1035	2165
Number of Events	92	30	17	27
Incidence per 1000 person-years (95%CI)	10.0(8.2-12.3)	10.8(7.6-15.4)	16.4(10.3-26.3)	12.5(8.6-18.1)
Crude HR	0.90(0.59-1.36)	-ref-	1.32(0.72-2.42)	-ref-
Adjusted HR	1.17(0.70-1.96)	-ref-	1.18(0.53-2.65)	-ref-
COMPARATOR: INSULIN				
	DPP4i	**Insulin**	**GLP1ra**	**Insulin**
Number of patients	10049	3600	854	2745
Person-years of follow-up	9878	1161	1033	919
Number of Events	97	24	14	19
Incidence per 1000 person-years (95%CI)	9.8(8.1-12)	20.7(13.9-30.8)	13.6(8.1-22.7)	20.7(13.3-32.3)
Crude HR	0.54(0.34-0.87)	-ref-	0.74(0.35-1.56)	-ref-
Adjusted HR	0.98(0.53-1.83)	-ref-	1.07(0.39-2.94)	-ref-

Table 3. Patient Characteristics of New-user GLP-1 Receptor Agonist Cohort Before and After Propensity Score Matching.

	GLP-1 Receptor Agonist New User Cohort Before Propensity Score Matching		GLP-1 Receptor Agonist New User Cohort After Propensity Score Matching	
	GLP-1RA (n=501)	**SU (n=16409)**	**GLP-1RA (n=488)**	**SU (n=488)**
Age in yrs (sd)	49.4(11.3)	57.8(12.9)	49.7(11.2)	49.2(12.6)
Female	204(40.7%)	6021(36.7%)	198(40.6%)	174(35.7%)
Measure of				
Least	40(8%)	1688(10.3%)	40(8.2%)	29(5.9%)
Most	56(11.2%)	1770(10.8%)	56(11.5%)	52(10.7%)
Unknown	240(47.9%)	6784(41.3%)	230(47.1%)	214(43.9%)
Diabetes duration in yrs (sd)	1.7(1.6)	1.2(1.6)	1.7(1.6)	1.7(1.8)
Body Mass Index>30	470(93.8%)	10481(63.9%)	458(93.9%)	452(92.6%)
Number of hospitalizations in year prior to cohort entry				
0	456(91%)	14170(86.4%)	445(91.2%)	437(89.5%)
1	29(5.8%)	1344(8.2%)	28(5.7%)	27(5.5%)
2	10(2%)	499(3%)	9(1.8%)	17(3.5%)
3+	6(1.2%)	396(2.4%)	6(1.2%)	7(1.4%)
Number of drugs in year prior to cohort entry				
0-4	17(3.4%)	1660(10.1%)	17(3.5%)	18(3.7%)
5-10	195(38.9%)	7899(48.1%)	192(39.3%)	208(42.6%)
11+	289(57.7%)	6850(41.7%)	279(57.2%)	262(53.7%)
HbA1c				
<6.5%	66(13.2%)	1085(6.6%)	62(12.7%)	66(13.5%)
6.5-7.5%	99(19.8%)	2593(15.8%)	97(19.9%)	99(20.3%)
7.5-9%	150(29.9%)	5357(32.6%)	145(29.7%)	134(27.5%)
9%+	179(35.7%)	7068(43.1%)	177(36.3%)	178(36.5%)
Unknown	7(1.4%)	306(1.9%)	7(1.4%)	11(2.3%)
e*GFR* <60	36(7.2%)	2821(17.2%)	35(7.2%)	40(8.2%)
Diagnoses in year prior to cohort entry				
Heart Failure	5(1%)	244(1.5%)	5(1%)	6(1.2%)
Hypertension	107(21.4%)	3398(20.7%)	106(21.7%)	104(21.3%)
Dyslipidemia	16(3.2%)	771(4.7%)	16(3.3%)	23(4.7%)
Ischemic heart	11(2.2%)	644(3.9%)	11(2.3%)	9(1.8%)
Peripheral	S	106(<1%)	S	S
Prescription drug use in year prior to cohort entry				
Metformin	457(91.2%)	13542(82.5%)	445(91.2%)	449(92%)
Acarbose	2(<1%)	7(<1%)	1(<1%)	1(<1%)
SGLT2 inhibitors	5(1%)	87(<1%)	5(1%)	5(1%)
Meglitinide	11(2.2%)	39(<1%)	10(2%)	10(2%)
Thiazolidinedione	38(7.6%)	376(2.3%)	38(7.8%)	41(8.4%)
Insulin	65(13%)	307(1.9%)	55(11.3%)	59(12.1%)
Hypnotic	32(6.4%)	1093(6.7%)	32(6.6%)	35(7.2%)
Mood	10(2%)	228(1.4%)	10(2%)	8(1.6%)
Anticonvulsant	33(6.6%)	682(4.2%)	31(6.4%)	32(6.6%)
Antipsychotics	12(2.4%)	507(3.1%)	**12(2.5%)**	12(2.5%)

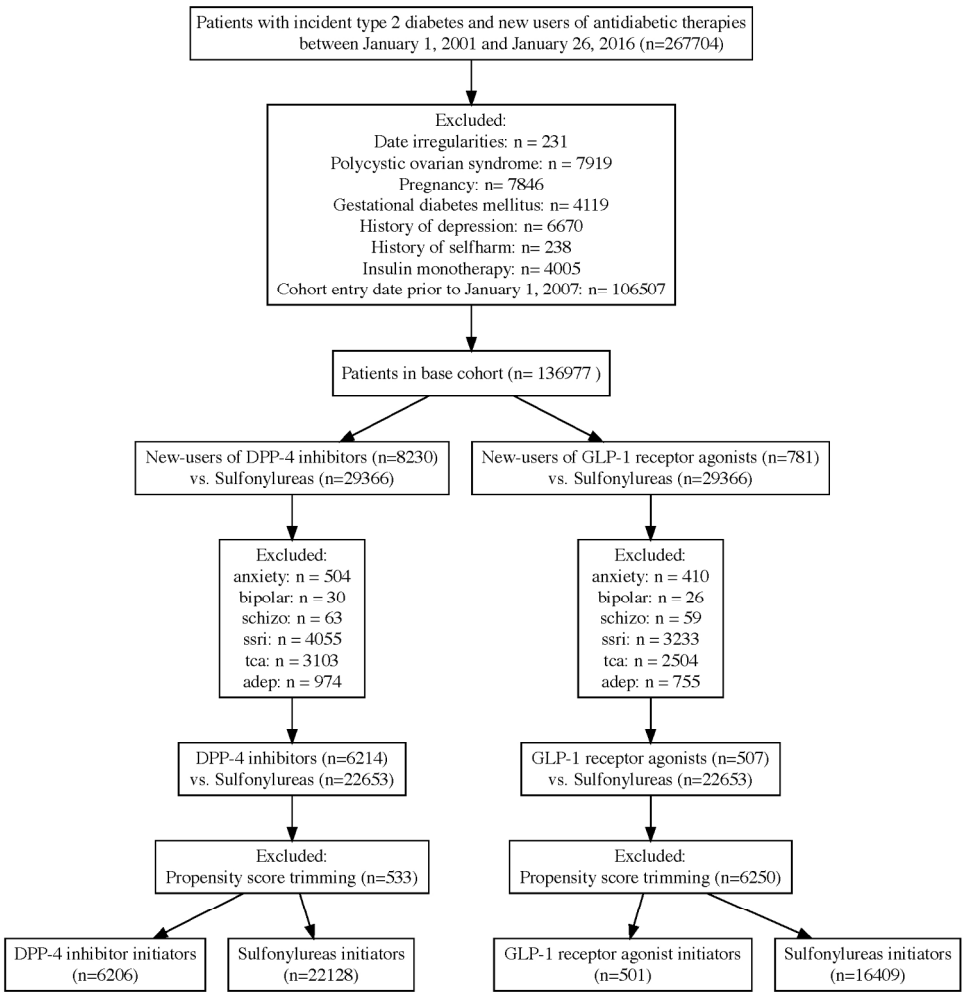
S = suppressed due to low number of events

FIGURES

Figure 1. Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

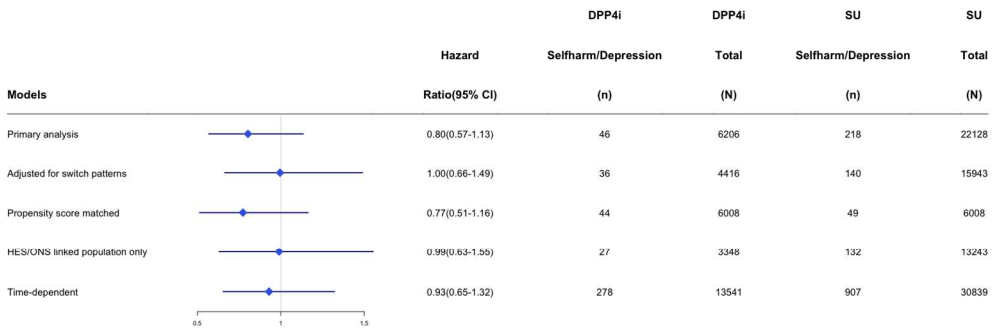
Figure 1. Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Figure 3. Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

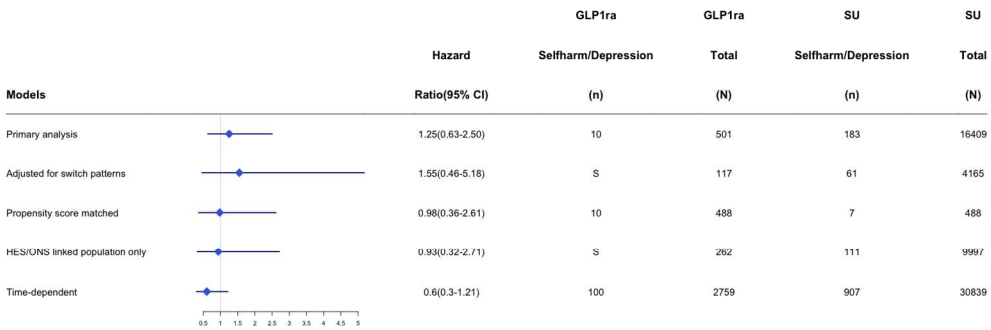


Flow Diagram to Identify Initiators of DPP-4 Inhibitors and Sulfonylureas (DPP-4 Inhibitor Cohort), and GLP-1 Receptor Agonists and Sulfonylureas (GLP-1 Receptor Agonist Cohort)

177x181mm (300 x 300 DPI)



Hazard Ratios and Number of Events within DPP-4 Inhibitor (DPP4i) and Sulfonylurea (SU) Users Across Sensitivity Analysis



Hazard Ratios and Number of Events within GLP-1 Receptor Agonist (GLP1ra) and Sulfonylurea (SU) Users Across Sensitivity Analysis

Supplementary Material

Appendix A: READ and ICD-10 Codes Used to Identify Depression

READ Code	Description
3004a	Depression
E2b..00	Depressive Disorder Nec
E204.00	Neurotic Depression Reactive Type
1b17.00	Depressed
Eu32z11	[X]Depression Nos
3004am	Mood Depressed
3004er	Reactive Depression
1b17.11	C/O - Feeling Depressed
3004l	Looking Depressed
E112.14	Endogenous Depression
E112.11	Agitated Depression
2960ad	Depression Agitated
E204.11	Postnatal Depression
E135.00	Agitated Depression
ICD-10 Code	Definition
F20.4	post-schizophrenic depression
F31.3	Bipolar affective disorder, current episode mild or moderate depression
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F32.0	Mild depressive episode
F32.1	Moderate depressive episode
F32.2	Severe depressive episode without psychotic symptoms
F32.3	Severe depressive episode with psychotic symptoms
F32.4	Depressive disorder, single episode in partial remission
F32.5	Depressive disorder, single episode in full remission
F32.8	Other depressive episodes
F32.9	Depressive episode, unspecified
F33.0	Recurrent depressive disorder, current episode

	mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.8	Other recurrent depressive disorders
F33.9	Recurrent depressive disorder, unspecified
F34.1	Dysthymia
F34.8	Other persistent mood [affective] disorders
F34.9	Persistent mood [affective] disorder, unspecified
F38.0	Other single mood [affective] disorders
F38.1	Other recurrent mood [affective] disorders
F38.8	Other specified mood [affective] disorders
F39	Unspecified mood [affective] disorder
F41.2	Mixed anxiety and depressive disorder
F99	Mental disorder, not elsewhere specified

Appendix B: READ and ICD-10 Codes Used to Identify Self-harm

READ Code	Description
SL..14	Overdose of biological substance
SL..15	Overdose of drug
SLHz.00	Drug and medicament poisoning not otherwise specified
TK..00	Suicide and self-inflicted injury
TK..11	Cause of overdose â€“ deliberate
TK..12	Injury â€“ self-inflicted
TK..13	Poisoning â€“ self-inflicted
TK..14	Suicide and self-harm
TK..15	Attempted suicide
TK..17	Para-suicide
TK0.00	Suicide + self-inflicted poisoning by solid/liquid substances
TK00.00	Suicide + self-inflicted poisoning by analgesic/antipyretic
TK01.00	Suicide + self-inflicted poisoning by barbiturates
TK01000	Suicide and self-inflicted injury by amylobarbitone
TK01100	Suicide and self-inflicted injury by barbitone
TK01400	Suicide and self-inflicted injury by phenobarbitone
TK02.00	Suicide + self-inflicted poisoning by other sedatives/hypnotics
TK03.00	Suicide + self-inflicted poisoning tranquillizer/psychotropic
TK04.00	Suicide + self-inflicted poisoning by other drugs/medicines

TK05.00	Suicide + self-inflicted poisoning by drug or medicine not otherwise specified
TK06.00	Suicide + self-inflicted poisoning by agricultural chemical
TK07.00	Suicide + self-inflicted poisoning by corrosive/caustic substance
TK0z.00	Suicide + self-inflicted poisoning by solid/liquid substance not otherwise specified
TK1.00	Suicide + self-inflicted poisoning by gases in domestic use
TK10.00	Suicide + self-inflicted poisoning by gas via pipeline
TK11.00	Suicide + self-inflicted poisoning by liquified petrol gas
TK1y.00	Suicide and self-inflicted poisoning by other utility gas
TK1z.00	Suicide + self-inflicted poisoning by domestic gases not otherwise specified
TK2.00	Suicide + self-inflicted poisoning by other gases and vapours
TK20.00	Suicide + self-inflicted poisoning by motor vehicle exhaust gas
TK21.00	Suicide and self-inflicted poisoning by other carbon monoxide
TK2z.00	Suicide + self-inflicted poisoning by gases and vapours not otherwise specified
TK3.00	Suicide + self-inflicted injury by hang/strangulate/suffocate
TK30.00	Suicide and self-inflicted injury by hanging
TK31.00	Suicide + self-inflicted injury by suffocation by plastic bag
TK3y.00	Suicide + self-inflicted injury by other means than hang/strangle/suffocate
TK3z.00	Suicide + self-inflicted injury by hang/strangle/suffocate not otherwise specified
TK4.00	Suicide and self-inflicted injury by drowning
TK5.00	Suicide and self-inflicted injury by firearms and explosives
TK51.00	Suicide and self-inflicted injury by shotgun
TK52.00	Suicide and self-inflicted injury by hunting rifle
TK54.00	Suicide and self-inflicted injury by other firearm
TK5z.00	Suicide and self-inflicted injury by firearms/explosives not otherwise specified
TK6.00	Suicide and self-inflicted injury by cutting and stabbing
TK60.00	Suicide and self-inflicted injury by cutting
TK60100	Self-inflicted lacerations to wrist
TK60111	Slashed wrists self-inflicted
TK61.00	Suicide and self-inflicted injury by stabbing
TK6z.00	Suicide and self-inflicted injury by cutting and stabbing not otherwise specified
TK7.00	Suicide and self-inflicted injury by jumping from high place
TK70.00	Suicide + self-inflicted injury â€“ jump from residential premises
TK71.00	Suicide + self-inflicted injury â€“ jump from other manmade structure
TK72.00	Suicide + self-inflicted injury â€“ jump from natural sites
TK7z.00	Suicide + self-inflicted injury â€“ jump from high place not otherwise specified
TKx.00	Suicide and self-inflicted injury by other means
TKx0.00	Suicide + self-inflicted injury â€“ jump/lie before moving object
TKx0000	Suicide + self-inflicted injury â€“ jumping before moving object
TKx1.00	Suicide and self-inflicted injury by burns or fire
TKx2.00	Suicide and self-inflicted injury by scald
TKx3.00	Suicide and self-inflicted injury by extremes of cold

TKx4.00	Suicide and self-inflicted injury by electrocution
TKx5.00	Suicide and self-inflicted injury by crashing motor vehicle
TKx6.00	Suicide and self-inflicted injury by crashing of aircraft
TKx7.00	Suicide and self-inflicted injury caustic substance
TKxy.00	Suicide and self-inflicted injury by other specified means
TKxz.00	Suicide and self-inflicted injury by other means not otherwise specified
TKy.00	Late effects of self-inflicted injury
TKz.00	Suicide and self-inflicted injury not otherwise specified
U2..00	[X]Intentional self-harm
U2..11	[X]Self-inflicted injury
U2..12	[X]Injury â€“ self-inflicted
U2..13	[X]Suicide
U2..14	[X]Attempted suicide
U2..15	[X]Para-suicide
U20.00	[X]Intentional self-poisoning/exposure to noxious substances
U20.11	[X]Deliberate drug overdose/other poisoning
U200.00	[X]Intentional self-poisoning/exposure to non-opioid analgesic
U200.11	[X]Overdose â€“ paracetamol
U200.12	[X]Overdose â€“ ibuprofen
U200.13	[X]Overdose â€“ aspirin
U200000	[X]Intentional self-poisoning/exposure to non-opioid analgesic at home
U200100	[X]Intentional self-poisoning non-opioid analgesic at residential institution
U200400	[X]Intentional self-poisoning non-opioid analgesic in street/highway
U200500	[X]Intentional self-poisoning non-opioid analgesic trade/service area
U200y00	[X]Intentional self-poisoning non-opioid analgesic other specified place
U200z00	[X]Intentional self-poisoning non-opioid analgesic unspecifified place
U201.00	[X]Intentional self-poisoning/exposure to antiepileptic
U201000	[X]Intentional self-poisoning/exposure to antiepileptic at home
U201z00	[X]Intentional self-poisoning antiepileptic unspecified place
U202.00	[X]Intentional self-poisoning/exposure to sedative hypnotic
U202.11	[X]Overdose â€“ sleeping tablets
U202.12	[X]Overdose â€“ diazepam
U202.13	[X]Overdose â€“ temazepam
U202.15	[X]Overdose â€“ nitrazepam
U202.16	[X]Overdose â€“ benzodiazepine
U202.17	[X]Overdose â€“ barbiturate
U202.18	[X]Overdose â€“ amobarbital
U202000	[X]Intentional self-poisoning /exposure to sedative hypnotic at home
U202400	[X]Intentional self-poisoning sedative hypnotic in street/highway
U202y00	[X]Intentional self-poisoning sedative hypnotic other specified place
U202z00	[X]Intentional self-poisoning sedative hypnotic unspecified place
U204.00	[X]Intentional self-poisoning/exposure to psychotropic drug
U204.11	[X]Overdose â€“ antidepressant

U204.12	[X]Overdose â€“ amitriptyline
U204.13	[X]Overdose â€“ SSRI
U204000	[X]Intentional self-poisoning /exposure to psychotropic drug at home
U204100	[X]Intentional self-poisoning psychotropic drug at residential institution
U204y00	[X]Intentional self-poisoning psychotropic drug other specified place
U204z00	[X]Intentional self-poisoning psychotropic drug unspecified place
U205000	[X]Intentional self-poisoning/exposure to narcotic drug at home
U205y00	[X]Intentional self-poisoning narcotic drug other specified place
U205z00	[X]Intentional self-poisoning narcotic drug unspecified place
U206.00	[X]Intentional self-poisoning/exposure to hallucinogen
U206400	[X]Intentional self-poisoning hallucinogen in street/highway
U207.00	[X]Intentional self-poisoning/exposure to other autonomic drug
U207000	[X]Intentional self-poisoning/exposure to other autonomic drug at home
U207z00	[X]Intentional self-poisoning other autonomic drug unspecified place
U208.00	[X]Intentional self-poisoning/exposure to other/unspecified drug/ medicament
U208400	[X]Intentional self-poisoning other/unspecified drug/medication in street/highway
U208y00	[X]Intentional self-poisoning other/unspecified drug/medication other specified place
U208z00	[X]Intentional self-poisoning other/unspecified drug/medication unspecified place
U20A.00	[X]Intentional self-poisoning organic solvent
U20A.11	[X]Self-poisoning from glue solvent
U20A000	"[X]Intentional self-poisoning organic solvent
U20A400	"[X]Intentional self-poisoning organic solvent
U20Az00	"[X]Intentional self-poisoning organic solvent
U20B.00	[X]Intentional self-poisoning/exposure to other gas/vapour U20B.11 [X]Self carbon monoxide poisoning
U20B000	[X]Intentional self-poisoning/exposure to other gas/vapour at home
U20B200	[X]Intentional self-poisoning other gas/vapour school/public admin area
U20By00	[X]Intentional self-poisoning other gas/vapour other specified place
U20Bz00	[X]Intentional self-poisoning other gas/vapour unspecified place
U20C.00	[X]Intentional self-poisoning/exposure to pesticide
U20C.11	[X]Self-poisoning with weedkiller
U20C.12	[X]Self-poisoning with paraquat
U20C000	[X]Intentional self-poisoning/exposure to pesticide at home
U20Cy00	[X]Intentional self-poisoning pesticide other specified place
U20y.00	[X]Intentional self-poisoning/exposure to unspecified chemical
U20y000	[X]Intentional self-poisoning/exposure to unspecified chemical at home
U20y200	[X]Intentional self-poisoning unspecified chemical school/public admin area
U20yz00	[X]Intentional self-poisoning unspecified chemical unspecified place
U21.00	[X]Intentional self-harm by hanging/strangulation/suffocation
U210.00	[X]Intentional self-harm by hanging/strangulation/suffocation at home

U211.00	[X]Intentional self-harm by hanging/strangulation/suffocation occurrence at residential institution
U21y.00	[X]Intentional self-harm by hanging/strangulation/suffocation other specified place
U21z.00	[X]Intentional self-harm by hanging/strangulation/suffocation unspecified place
U22.00	[X]Intentional self-harm by drowning and submersion
U221.0	[X]Intentional self-harm by drowning/submersion occurrence at residential institution
U22y.00	[X]Intentional self-harm by drowning/submersion occurrence at other specified place
U22z.00	[X]Intentional self-harm by drowning/submersion occurrence at unspecified place
U24.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge
U241.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge occurrence at residential institution
U242.00	[X]Intentional self-harm by rifle shotgun/larger firearm discharge in school/public admin area
U25.00	[X]Intentional self-harm by other/unspecified firearm discharge
U250.00	[X]Intentional self-harm other/unspecif firearm discharge occurrence at home
U26.00	[X]Intentional self-harm by explosive material
U27.00	[X]Intentional self-harm by smoke
U270.00	[X]Intentional self-harm by smoke fire/flames occurrence at home
U274.00	[X]Intentional self-harm by smoke fire/flame occurrence in street/highway
U27z.00	[X]Intentional self-harm by smoke fire/flames occurrence in unspecified place
U28.00	[X]Intentional self-harm by steam hot vapours/hot objects
U280.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence at home
U28z.00	[X]Intentional self-harm by steam hot vapours/hot objects occurrence in unspecified place
U29.00	[X]Intentional self-harm by sharp object
U290.00	[X]Intentional self-harm by sharp object occurrence at home
U291.00	[X]Intentional self-harm by sharp object occurrence at residential institution
U294.00	[X]Intentional self-harm by sharp object occurrence in street/highway
U29y.00	[X]Intentional self-harm by sharp object occurrence at other specified place
U29z.00	[X]Intentional self-harm by sharp object occurrence at unspecified place
U2A.00	[X]Intentional self-harm by blunt object
U2A0.00	[X]Intentional self-harm by blunt object occurrence at home
U2A1.00	[X]Intentional self-harm by blunt object occurrence at residential institution
U2A3.00	[X]Intentional self-harm by blunt object occurrence at sports/athletic area
U2B.00	[X]Intentional self-harm by jumping from a high place
U2B0.00	[X]Intentional self-harm by jumping from high place occurrence at home
U2B4.00	[X]Intentional self-harm by jumping from high place occurring in street/highway
U2B6.00	[X]Intentional self-harm by jumping from high place industrial/construction area

U2By.00	[X]Intentional self-harm by jumping from high place occurrence other specified place
U2Bz.0	0
U2C.00	[X]Intentional self-harm by jumping/lying before moving object
U2C1.00	[X]Intentional self-harm by jumping/lying before moving object occurrence at residential institution
U2C4.00	[X]Intentional self-harm by jumping/lying before moving object occurrence in street/highway
U2Cy.00	[X]Intentional self-harm by jumping/lying before moving object occurrence other specified place
U2D.00	[X]Intentional self-harm by crashing of motor vehicle
U2D0.00	[X]Intentional self-harm by crashing of motor vehicle occurrence at home
U2D4.00	[X]Intentional self-harm by crashing of motor vehicle occurrence in street/highway
U2D6.00	[X]Intentional self-harm by crashing of motor vehicle occurrence industrial/construction area
U2E.00 [X]Self-mutilation	
U2y.00	[X]Intentional self-harm by other specified means
U2y0.00	[X]Intentional self-harm by other specified means occurrence at home
U2y1.00	[X]Intentional self-harm by other specified means occurrence at residential institution
U2yz.00	[X]Intentional self-harm by other specif means occurrence at unspecified place
U2z.00	[X]Intentional self-harm by unspecified means
U2z0.00	[X]Intentional self-harm by unspecified means occurrence at home
U2z2.00	[X]Intentional self-harm by unspecified means occurrence school/institution/public administrative area
U2zy.00	[X]Intentional self-harm by unspecified means occurrence other specified place
U2zz.00	[X]Intentional self-harm by unspecified means occurrence at unspecified place
U30.11	[X]Deliberate drug poisoning
U41.00	[X]Hanging strangulation + suffocation undetermined intent
U44.00	[X]Rifle shotgun + larger firearm discharge undetermined intent
U45.00	[X]Other + unspecified firearm discharge undetermined intent
U4B.00	[X]Falling jumping/pushed from high place undetermine intent
U4Bz.00	[X]Fall jump/push from high place undetermine intent occurring at unspecified place
U72.00	[X]Sequelae of intentional self-harm assault + event of undetermined intent
U720.00	[X]Sequelae of intentional self-harm
ZRLfC12	Health of the Nation Outcome Scales item 2 â€“ nonaccidental self-injury
ZX..00	Self-harm
ZX..11	Self-damage
ZX1.00	Self-injurious behaviour
ZX1.12	SIB â€“ self-injurious behaviour
ZX1.13	Deliberate self-harm
ZX11.00	Biting self

ZX11.11	Bites self
ZX12.00	Burning self
ZX13.00	Cutting self
ZX13.11	Cuts self
ZX15.00	Drowning self
ZX18.00	Hanging self
ZX19.00	Hitting self
ZX19100	Punching self
ZX19200	Slapping self
ZX1B.00	Jumping from height
ZX1B100	Jumping from building
ZX1B200	Jumping from bridge
ZX1B300	Jumping from cliff
ZX1C.00	Nipping self
ZX1E.00	Pinching self
ZX1G.00	Scratches self
ZX1H.00	Self-asphyxiation
ZX1H100	Self-strangulation
ZX1H200	Self-suffocation
ZX1I.00	Self-scalding
ZX1J.00	Self-electrocution
ZX1K.00	Self-incineration
ZX1K.11	Setting fire to self
ZX1K.12	Setting self alight
ZX1L.00	Self-mutilation
ZX1L100	Self-mutilation of hands
ZX1L200	Self-mutilation of genitalia
ZX1L300	Self-mutilation of penis
ZX1L600	Self-mutilation of ears
ZX1LD00	[X]Self mutilation
ZX1M.00	Shooting self
ZX1N.00	Stabbing self
ZX1Q.00	Throwing self in front of train
ZX1Q.11	Jumping under train
ZX1R.00	Throwing self in front of vehicle
ZX1S.00	Throwing self onto floor
ICD-10code	Description
X60	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics
X61	Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics

	[hallucinogens], not elsewhere classified
X63	Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system
X64	Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances
X65	Intentional self-poisoning by and exposure to alcohol
X66	Intentional self-poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours
X67	Intentional self-poisoning by and exposure to other gases and vapours
X68	Intentional self-poisoning by and exposure to pesticides
X69	Intentional self-poisoning by and exposure to other and unspecified chemicals and noxious substances
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X73	Intentional self-harm by rifle, shotgun and larger firearm discharge
X74	Intentional self-harm by other and unspecified firearm discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X77	Intentional self-harm by steam, hot vapours and hot objects
X78	Intentional self-harm by sharp object
X79	Intentional self-harm by blunt object
X80	Intentional self-harm by jumping from a high place
X81	Intentional self-harm by jumping or lying before moving object
X82	Intentional self-harm by crashing of motor vehicle
X83	Intentional self-harm by other specified means
X84	Intentional self-harm by unspecified means
Y10	Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent
Y11	Poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent
Y12	Poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent
Y13	Poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent
Y14	Poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent
Y15	Poisoning by and exposure to alcohol, undetermined intent
Y16	Poisoning by and exposure to organic solvents and halogenated hydrocarbons and their vapours, undetermined intent
Y17	Poisoning by and exposure to other gases and vapours, undetermined intent
Y18	Poisoning by and exposure to pesticides, undetermined intent
Y19	Poisoning by and exposure to other and unspecified chemicals and noxious substances, undetermined intent
Y20	Hanging, strangulation and suffocation, undetermined intent

Y21	Drowning and submersion, undetermined intent
Y22	Handgun discharge, undetermined intent
Y23	Rifle, shotgun and larger firearm discharge, undetermined intent
Y24	Other and unspecified firearm discharge, undetermined intent
Y25	Contact with explosive material, undetermined intent
Y26	Exposure to smoke, fire and flames, undetermined intent
Y27	Contact with steam, hot vapours and hot objects, undetermined intent
Y28	Contact with sharp object, undetermined intent
Y29	Contact with blunt object, undetermined intent
Y30	Falling, jumping or pushed from a high place, undetermined intent
Y31	Falling, lying or running before or into moving object, undetermined intent
Y32	Crashing of motor vehicle, undetermined intent
Y33	Other specified events, undetermined intent
Y34	Unspecified event, undetermined intent

Appendix C. Covariates Forced into the High Density Propensity Score

All covariates assessed in the 365 days prior to study index date
Age at index date
Alcohol Abuse [Never, Former, Current, Unknown]
BMI
Duration of treated diabetes [time between first oral antidiabetic drug and study index date]
History of: Cirrhosis Congestive heart failure Hypertension Hyperlipidemia Ischemic heart disease Peripheral heart disease
Number of hospitalizations
Most recent HbAlc value to index date
Number of distinct prescription drugs
Prior use of benzodiazepines or other hypnotics, antipsychotics, levothyroxine or triiodothyrinine, anticonvulsants, or mood stabilizers
Sex
Smoking status [Never, Former, Current, Unknown]
Socioeconomic status [quintiles of Index of Mulitiple Deprivation]
Use of other antidiabetic agents
Year of cohort entry

Appendix D. Measures of frequency and association for depression among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6207	22218		502	16728
Person-years follow-up	5591	18683		549	13628
Number of events	45	215		10	182
Incidence per 1000 person-years (95%CI)	8.0 (6.0-10.8)	11.5 (10.1-13.2)		18.2 (10-33.5)	13.4 (11.6-15.4)
Crude Hazard Ratio (95% CI)	0.70 (0.50-0.96)	-ref-		1.39 (0.74-2.63)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.57-1.14)	-ref-		1.22 (0.61-2.42)	-ref-

S = suppressed due to low number of events

Appendix E. Measures of frequency and association for self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts

	DPP4i	SU		GLP1ra	SU
Number of patients	6211	22180		502	16632
Person-years follow-up	5632	18839		563	13696
Number of events	S	5		S	S
Incidence per 1000 person-years (95%CI)	S	0.3 (0.1-0.6)		S	S
Crude Hazard Ratio (95% CI)	0.66 (0.08-5.69)	-ref-		S	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.07-8.21)	-ref-		S	-ref-

S = suppressed due to low number of events

Appendix F. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are matched 1:1 by propensity score.

	DPP4i	SU		GLP1ra	SU
Number of patients	6008	6008		488	488
Person-years follow-up	548	4488		529	349
Number of events	44	49		10	7
Incidence per 1000 person-years (95%CI)	8.0 (6-10.8)	10.9 (8.3-14.4)		18.9 (10.4-34.8)	20.1 (9.9-41.3)
Crude Hazard Ratio (95% CI)	0.75 (0.50-1.13)	-ref-		0.99 (0.37-2.61)	-ref-
Adjusted Hazard Ratio (95% CI)	0.77 (0.51-1.16)	-ref-		0.98 (0.36-2.61)	-ref-

Appendix G. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are adjusted for pattern of glucose-lowering therapy.

	DPP4i	SU		GLP1RA	SU
Number of patients	4416	15943		117	4165
Person-years follow-up	3743	12614		90	3327
Number of events	36	140		S	61
Incidence per 1000 person-years (95%CI)	9.6 (7-13.3)	11.1 (9.4-13.1)		33.4 (12.1-97.5)	18.3 (14.3-23.6)
Crude Hazard Ratio (95% CI)	0.86 (0.60-1.24)	-ref-		1.82 (0.57-5.80)	-ref-
Adjusted Hazard Ratio (95% CI)	1.00 (0.66-1.49)	-ref-		1.55 (0.46-5.18)	-ref-

S = suppressed due to low number of events

Appendix H. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to only those with HES/ONS linked data.

	DPP4i	SU		GLP1ra	SU
Number of patients	3348	13243		262	9997
Person-years follow-up	2841	10762		290	7904
Number of events	27	132		S	111
Incidence per 1000 person-years (95%CI)	9.5 (6.5-13.8)	12.3 (10.3-14.5)		13.8 (5.6-35.3)	14 (11.7-16.9)
Crude Hazard Ratio (95% CI)	0.78 (0.51-1.17)	-ref-		1.00 (0.37-2.72)	-ref-
Adjusted Hazard Ratio (95% CI)	0.99(0.63-1.55)	-ref-		0.93 (0.32-2.71)	-ref-

Appendix I. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when patients are restricted to second-line therapy after metformin monotherapy.

	DPP4i	SU		GLP1ra	SU
Number of patients	1255	4612		65	2112
Person-years follow-up	1191	3601		47	1680
Number of events	11	48		S	29
Incidence per 1000 person-years (95%CI)	9.2 (5.2-16.5)	13.3 (10.1-17.7)		43(13.3-155.3)	17.3 (12-24.8)
Crude Hazard Ratio (95% CI)	0.71 (0.37-1.38)	-ref-		2.49(0.59-10.45)	-ref-
Adjusted Hazard Ratio (95% CI)	0.67 (0.34-1.34)	-ref-		1.92(0.44-8.31)	-ref-

S = suppressed due to low number of events

Appendix J. Measures of frequency and association for depression or self-harm among DPP-4 inhibtor and GLP-1 receptor agonist cohorts when BMI categories (in addition to hdps deciles) were added to the Cox proportional regression model.

	DPP4i	SU		GLP1ra	SU
Number of patients	6206	22128		501	16409
Person-years follow-up	5589	18596		549	13418
Number of events	46	218		10	183
Incidence per 1000 person-years (95%CI)	8.2 (6.2-11)	11.7 (10.3-13.4)		18.2 (10-33.5)	13.6 (11.8-15.8)
Crude Hazard Ratio (95% CI)	0.70 (0.51-0.96)	-ref-		1.36 (0.72-2.58)	-ref-
Adjusted Hazard Ratio (95% CI)	0.81 (0.58-1.15)	-ref-		1.25 (0.63-2.51)	-ref-

S = suppressed due to low number of events

Appendix K. Time-dependent Cox regression for DPP-4 inhibitor monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
DPP-4i monotherapy	-0.07	0.93	0.65	1.32	0.18	0.69
DPP-4i/SU	-0.53	0.59	0.34	1.02	0.28	0.06
DPP-4i/Other	-0.16	0.85	0.70	1.04	0.10	0.11
DPP-4i/SU/Other	-0.13	0.88	0.68	1.14	0.13	0.33

*Adjusted for deciles of hdps

Appendix L. Time-dependent Cox regression for GLP-1 receptor agonist (GLP1ra) monotherapy and combination therapies Vs. Sulfonylurea (SU) monotherapy

Exposure vs. SU monotherapy	Coef	*Adjusted HR	Lower .95	Upper .95	Se (coef)	Pr (>|z|)
GLP1ra monotherapy	-0.51	0.60	0.30	1.21	0.36	0.15
GLP1ra /SU	0.45	1.57	0.78	3.18	0.36	0.21
GLP1ra /Other	0.14	1.16	0.88	1.52	0.14	0.31
GLP1ra /SU/Other	-0.31	0.73	0.47	1.15	0.23	0.18

*Adjusted for deciles of hdps

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Cohort in title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Structured abstract provided**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Introduction – paragraphs 1 and 2**
Objectives	3	State specific objectives, including any prespecified hypotheses **Introduction – paragraph 3**
Methods		
Study design	4	Present key elements of study design early in the paper **Methods, Study Design and Data Sources section, paragraph 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Methods, Study Design and Data Sources section, paragraph 1**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Methods, Study Cohort section, paragraph 1**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Methods, Exposure and Outcome Definitions section**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Methods, Exposure and Outcome Definitions section** **Supplemental appendix**
Bias	9	Describe any efforts to address potential sources of bias **Methods, Statistical Analysis section, paragraphs 2 and 3**
Study size	10	Explain how the study size was arrived at **Figure 1**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Methods, Exposure and Outcome Definitions section** **Methods, Statistical Analysis section**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **Methods, Statistical Analysis section**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram **Figure 1 is a flow diagram**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) **Table 3** **Results section**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Table 3** **Results section** **Supplemental appendix**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Results section** **Table 3**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Results section, paragraph 5** **Figure 2** **Figure 3** **Supplemental appendix**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Discussion section, paragraph 1**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Discussion section, paragraph 5**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Discussion section, final paragraph**
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Funding support**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.