Association between GLP-1 receptor agonist use and worsening mental illness in people with depression and anxiety in Sweden: a national cohort study

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Summary

Background People with diabetes have an elevated risk of developing depression, anxiety, and suicide. GLP-1 receptor agonists are licensed to treat diabetes and obesity, but data on whether these medications alleviate or exacerbate anxiety, depression, and self-harm are mixed. We studied the risk of worsening mental illness in people already diagnosed with depression, anxiety, or both who were prescribed antidiabetic medications including GLP-1 receptor agonists.

Methods The study cohort, identified from national Swedish electronic health registers, included people with a diagnosis of depression or anxiety disorder who used any antidiabetic medication between the years 2009 and 2022. GLP-1 receptor agonists, individually and as a group, were compared with non-use of GLP-1 receptor agonists and directly with other second-line antidiabetic medications. A within-individual design was used for all comparisons to reduce confounding, comparing periods of use versus periods of non-use of a medication in the same individual. The primary outcome was worsening of mental illness, defined as a composite of psychiatric hospitalisation; sick leave from work for more than 14 days for psychiatric reasons; hospitalisation due to self-harm; or death by suicide. Secondary outcomes were worsening of depression or anxiety, analysed separately, worsening of substance use disorder, and self-harm. Within-individual stratified Cox models with adjusted hazard ratios (aHRs) and 95% CIs were used. A person with related lived experience was involved in the design and write-up of this study.

Findings The cohort included 95 490 people (56 976 [59·7%] female and 38 514 [40·3%] male) with a mean age of 50·6 years (SD 12·3). Ethnicity data were not available. GLP-1 receptor agonists were used by 22 480 individuals during the follow-up period. Compared with non-use of GLP-1 receptor agonists, semaglutide (aHR 0·58 [95% CI 0·51–0·65]) and liraglutide (0·82 [0·76–0·89]) were associated with lower risk of worsening mental illness, whereas exenatide (1·01 [0·69–1·46]) and dulaglutide (1·01 [0·85–1·20]) were not. Semaglutide was associated with a decreased risk of worsening depression (0·56 [0·44–0·71]), of worsening anxiety (0·62 [0·52–0·73]), and of worsening substance use disorder (0·53 [0·35–0·80]). Liraglutide was associated only with lower risk of worsening depression (0·74 [0·64–0·87]). GLP-1 receptor agonists as a group were associated with a reduced risk of self-harm (0·56 [0·34–0·92]).

Interpretation For anxiety and depression that co-occur with diabetes and obesity, semaglutide and, to a lesser extent, liraglutide might be useful dually effective therapeutic options. Randomised controlled trials evaluating these findings are warranted.

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Introduction

GLP-1 receptor agonists (also known as incretin mimetics) are licensed for the treatment of diabetes and obesity in many countries and mimic the endogenous GLP-1 hormone by inhibiting glucagon and stimulating insulin release.[1] GLP-1 receptor agonists also increase satiety or reduce hunger and cravings.[1] In the USA, over 15 million people (6%) are now estimated[2] to be officially prescribed GLP-1 receptor agonists, although with online and overseas supplies this number might be an underestimate.

People with diabetes are more likely than the general population to develop depression and anxiety[3,4] and have an elevated risk of death by suicide.[5] There appears to be a circular relationship between metabolic dysregulation—such as in diabetes or obesity—and anxiety and depression.[6,7] Furthermore, depression and anxiety are now among the leading reasons[8] for health-related sick leave.

Recent research[1,9–12] has suggested that GLP-1 receptor agonists might have neuropsychiatric benefits for cognition, substance misuse or addiction, and mood

Research in context

Evidence before this study

People with diabetes or obesity are more likely than the general population to suffer from depression and anxiety. Whether GLP-1 receptor agonists reduce or exacerbate this risk is uncertain. Our systematic search of PubMed and Google Scholar using the terms "GLP-1", "GLP-1RA", "depression", "anxiety", and "suicide", with no language restrictions, from inception to Sept 30, 2025, found for the last 12 months alone eight relevant systematic reviews and four pertinent meta-analyses. Adverse psychiatric outcomes associated with GLP-1 receptor agonists were depression, anxiety, and suicidal ideation in pharmacovigilance and observational studies, leading to regulatory concerns. Individual studies found mixed results on these psychiatric outcomes. However, the latest large meta-analytic reviews including placebo data have been more reassuring, noting no increased risk of suicide or depression severity in all studies of GLP-1 receptor agonists.

Added value of this study

This is the first study to show that people using GLP-1 receptor agonists were less likely to have worsening mental illness, including less worsening of depression, anxiety, and self-harm, when compared to periods when the same people were not using GLP-1 receptor agonists. Individual GLP-1 receptor agonists were differentially associated, in this national cohort studied over a long period, with a reduced risk of hospitalisation and sick leave from work, as well as decreased risk of worsening depression and anxiety outcomes. This finding implies that this is not a medication class effect. Semaglutide was the single most effective GLP-1 receptor agonist among those studied, followed by liraglutide. GLP-1 receptor agonists as a group were associated with a reduced risk of self-harm.

Implications of all the available evidence

GLP-1 receptor agonists might prevent worsening of depression and anxiety. Randomised controlled trials testing these associations of dual effectiveness are warranted.

disorders, although other contemporary data[13] found an increased risk of anxiety, depression, and suicide in a large cohort of people using GLP-1 receptor agonists. These conflicting findings might be due to selection bias if people using GLP-1 receptor agonists are inherently different to the comparison group.

To avoid the aforementioned selection bias, we used a within-individual design whereby each person acts as their own control, which has previously[12,14] been accepted as a way to reduce confounding arising from differences in individual patient characteristics or psychiatric profiles. We studied the risk of worsening mental illness in people already diagnosed with depressive or anxiety disorders who were prescribed various antidiabetic medications, including GLP-1 receptor agonists. Within an individual, time periods in which GLP-1 receptor agonists were used were compared with periods in which GLP-1 receptor agonists were not used or when other antidiabetic medications were prescribed, using national Swedish register-based data on individuals with depression or anxiety disorders.

Methods

Study design and population

We involved a person with related lived experience in the design and write-up of this study. Ethnicity data were not available. The project was approved by the Regional Ethical Review Board of the Karolinska Institutet (2007/762-31 and 2021-06441-02). Informed consent is not required in Sweden for register-based studies in which there is no patient contact.

National Swedish electronic health registers were used to obtain and combine data through personal pseudonymised identification numbers. Sweden has a decentralised, government-funded health-care system, available to all people free of charge, with private or insurance funded health care being a rarity. The Swedish National Patient Register for inpatient and specialist outpatient visits, as well as the Microdata for Analysis of the Social Insurance (MiDAS) register containing data on sick leave (absence from work due to ill health) and disability pension diagnoses, were used to identify study participants.

The study cohort included only those people with a diagnosis of depression (ICD-10 diagnostic codes F32–F33) or an anxiety disorder (F40–F43) who were using any non-insulin antidiabetic medication between the years 2009 and 2022. This period was chosen due to the availability of GLP-1 receptor agonists in Sweden and ended in 2022 due to availability of sick-leave data as an outcome. People with a previous diagnosis of schizophrenia-spectrum disorders (F20–F29) or bipolar disorder (F30–F31) were excluded, as these diagnoses represent more severe clinically different conditions. There were no other exclusion criteria.

Cohort entry was defined as the first diagnosis of depression or an anxiety disorder, or the start of the first antidiabetic medication, whichever came last. Follow-up ceased due to death, emigration, developing schizophrenia or bipolar disorder, or by Dec 31, 2022.

Exposures

The PRE2DUP method[15] was used to construct individual drug-use periods by modelling data from the Prescribed Drug Register. The exposures analysed were use of the most frequently prescribed GLP-1-receptor agonist

(Anatomical Therapeutic Chemical [ATC] code A10BJ), namely semaglutide; liraglutide; exenatide; and dulaglutide. A group category of all GLP-1 receptor agonists included was also constructed. Lixisenatide was excluded as it was rarely used. The main reference category for GLP-1 receptor agonists was non-use of all GLP-1 receptor agonist medications (appendix p 2).

To control for the severity of diabetes, we compared GLP-1 receptor agonists with the most-used other second-line antidiabetics after first-line metformin, namely the SGLT2 inhibitors empagliflozin (ATC code A10BK03) and dapagliflozin (A10BK01) and the DPP-4 inhibitor sitagliptin (A10BH01). In these analyses, only monotherapy with these second-line antidiabetics was included for head-to-head comparisons. Metformin use was allowed for all participants at any time, but time periods in which only one of the second-line treatments (namely liraglutide, semaglutide, empagliflozin, dapagliflozin, and sitagliptin) was in use were included in these analyses.

Outcomes

To capture the primary outcome of worsening mental illness in a comprehensive manner, we defined this outcome as a composite of psychiatric hospital admissions (F00–F99), sick leave from work (either full-time or part-time sickness absence for more than 14 days due to psychiatric reasons [F00–F99]), hospitalisation due to self-harm (X60–X84 or Y10–Y34), and death due to suicide. Hospitalisation and sick leave used codes for any psychiatric diagnosis to enable complete coverage for episodes of worsening mental health.

The secondary outcomes analysed (defined a priori) were worsening anxiety disorders (F40–F43); worsening depression (F32–F33); and worsening substance use disorder (F10–F19) in the study population with pre-existing anxiety or depression (or both), with worsening defined in the same way as for the primary outcome. This definition of worsening could also include a new diagnosis of depression in an individual who entered the study with anxiety, or vice versa. An additional a priori-defined secondary outcome was self-harm (hospital-treated self-harm, X60–X84 or Y10–Y34).

Statistical analysis

We used a within-individual design wherein each individual or person acts as their own control.[16,17] Cox regression models with fixed effects were used to calculate the within-individual risk of an outcome. Within-individual design minimises selection bias and automatically eliminates the effects of time-invariant characteristics (gender, baseline severity of illness, or other comorbid conditions) by comparing specific treatment periods within the same individuals. We adjusted for time-varying covariates, namely the temporal order of exposures (GLP-1 receptor agonist use *vs* non-use periods in the main analysis), time since cohort entry, and use of other antidiabetic medications, antipsychotics, mood stabilisers, medications for substance use disorders, and benzodiazepines and related drugs (appendix pp 6–8).

In the main model, periods of use of individual GLP-1 receptor agonists were compared with periods of non-use of GLP-1 receptor agonists within the same individuals. As a secondary comparison, periods of use of GLP-1 receptor agonists were compared with periods of use of other specific antidiabetic medications, also within the same individuals. Other a priori-defined secondary analyses were as follows: restricting analyses to the period after semaglutide received European Marketing Approval to ensure that time periods before that did not

See Online for appendix

	All (n=95 490)	GLP-1 receptor agonist use (n=22 480)	Semaglutide use (n=13 445)
Mean age at cohort entry, years	50·6 (12·3)	49·9 (10·9)	50·6 (10·6)
Gender			
Female	56 976 (59·7%)	14 216 (63·2%)	5387 (40·1%)
Male	38 514 (40·3%)	8264 (36·8%)	8058 (59·9%)
Educational level*			
Low	16 413 (17·2%)	3033 (13·5%)	1853 (13·8%)
Medium	41 290 (43·2%)	9817 (43·7%)	6189 (46·0%)
High	24 105 (25·2%)	6059 (27·0%)	3695 (27·5%)
Unknown	13 682 (14·3%)	3571 (15·9%)	1708 (12·7%)
Sick leave during follow-up			
Any	12 515 (13·1%)	2240 (10·0%)	1255 (9·3%)
Due to anxiety and depression	7954 (8·3%)	1556 (6·9%)	863 (6·4%)
Disability pension	7449 (7·8%)	439 (2·0%)	264 (2·0%)
Index episode			
Depression	52 385 (54·9%)	11 042 (49·1%)	6414 (47·7%)
Anxiety disorder	77 819 (81·5%)	17 976 (80·0%)	10 651 (79·2%)
Depression and anxiety disorder	34 714 (36·4%)	6538 (29·1%)	3620 (26·9%)
Substance use disorder	19 309 (20·2%)	3164 (14·1%)	1788 (13·3%)
Indication for antidiabetic use†			
Type 2 diabetes	80 613 (84·4%)	18 473 (82·2%)	9873 (73·4%)
Heart failure or renal failure	1880 (2·0%)	70 (0·3%)	22 (0·2%)
Obesity or weight loss	6836 (7·2%)	2596 (11·5%)	673 (5·0%)
Polycystic ovarian syndrome	1303 (1·4%)	61 (0·3%)	13 (0·1%)
Unknown comorbidities	4858 (5·1%)	1280 (5·7%)	386 (2·9%)
Antidiabetic use			
Metformin	59 142 (61·9%)	15 661 (69·7%)	10 533 (78·3%)
GLP-1 receptor agonist	22 480 (23·5%)	22 480 (100·0%)	13 445 (100·0%)
DPP-4 inhibitors	11 784 (12·3%)	4846 (21·6%)	3301 (24·6%)
SGLT-2 inhibitors	18 744 (19·6%)	8076 (35·9%)	5475 (40·7%)
Sulfonylureas	6344 (6·6%)	2665 (11·9%)	1683 (12·5%)
Insulin	21 238 (22·2%)	7541 (33·5%)	4600 (34·2%)

Data are mean (SD) or n (%). *Educational levels were defined as low for 0–9 years in education, medium for 9–12 years, or high for more than 12 years. †Probable indication for antidiabetic use was defined either as type 2 diabetes or "other"; in the "other" category were heart failure or renal failure, obesity or weight loss, polycystic ovarian syndrome versus not known; these conditions were recorded as diagnosis or as indication, stated in the free text of antidiabetic prescriptions.

Table: **Characteristics of study cohort overall, those who used any GLP-1 receptor agonists, and those who used semaglutide during the follow-up**

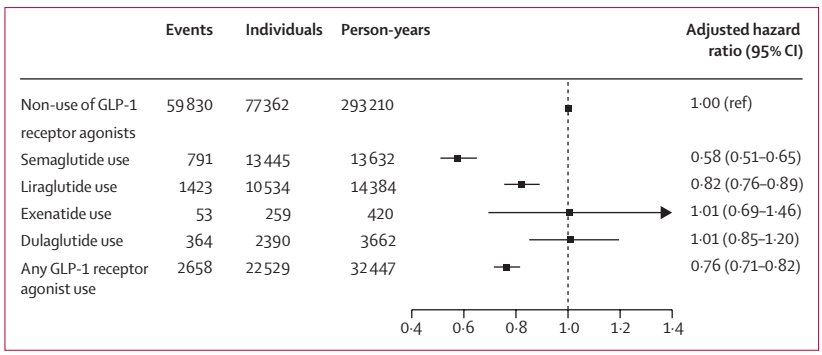

Figure 1: **Risk of worsening mental illness associated with GLP-1 receptor agonist use compared with non-use periods in a within-individual model**

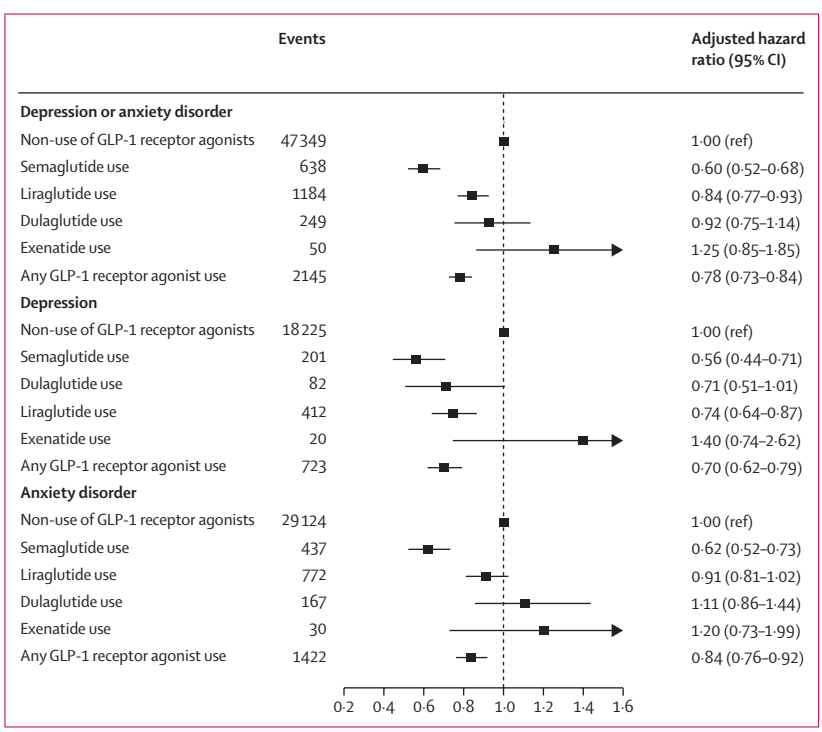

Figure 2: **Risk of worsening depression or anxiety disorder associated with GLP-1 receptor agonist use compared with non-use periods in a within-individual model**
Numbers of individuals and person-years are the same as in figure 1.

artificially affect the results; and omitting first 30 days and first 60 days from exposure and non-exposure periods to account for possible carryover effects from exposure to non-exposure periods, while acknowledging that pharmacological effects during the first days of exposure can be suboptimal.

In a post-hoc analysis, we restricted analysis to those who entered the cohort with antidiabetic medications other than GLP-1 receptor agonists to ensure that these people potentially using GLP-1 receptor agonists for weight loss or indications other than diabetes and their sequence of exposures (ie, first use and then non-use of GLP-1 receptor agonists) did not alter the results. In addition, the analysis of the main outcome was stratified by gender and by the type of index episode (depression, anxiety disorder, or both).

Results are presented as adjusted hazard ratios (aHRs) and 95% CIs. Exposures with fewer than ten events were excluded from the results. Data analyses were conducted from January to July, 2025, using SAS version 9.4.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The total cohort comprised 95 490 individuals, with the mean age at cohort entry being 50·6 years (SD 12·3). 56 976 (59·7%) of the study cohort were female and 38 514 (40·3%) were male (table). 77 819 (81·5%) individuals had a diagnosis of anxiety disorder, 52 385 (54·9%) had depression, and 34 714 (36·4%) had both conditions. The sociodemographic and socioeconomic characteristics of people using GLP-1 receptor agonists (n=22 480) did not differ from those of the total cohort, except that these individuals were less likely to be on disability pension (439 [2·0%] individuals) at cohort entry compared with the total cohort (7449 [7·8%]; table).

The mean follow-up period for the cohort was 5·2 years (SD 3·9). The primary outcome occurred in 32 638 people at least once. GLP-1 receptor agonists were used by 22 480 individuals (23·5% of the total cohort) during the follow-up period, of whom 13 445 (59·8%) were prescribed semaglutide and 10 534 (46·9%) were prescribed liraglutide. The median duration of use periods was 123 days (IQR 33–325; median 4 [2–8] use periods per person) for semaglutide and 61 days (IQR 21–200; median 6 [3–10] use periods per person) for liraglutide.

Periods of semaglutide use (aHR 0·58 [95% CI 0·51–0·65]) and liraglutide use (0·82 [0·76–0·89]) were associated with a decreased risk of worsening mental illness compared with time periods in which the same individuals did not use GLP-1 receptor agonists (figure 1; appendix pp 3–4). This association was not observed for exenatide (1·01 [0·69–1·46]) or dulaglutide (1·01 [0·85–1·20]). When semaglutide was compared directly with any other GLP-1 receptor agonist used by the same individual (among 3705 people who used both semaglutide and another GLP-1 receptor agonist during follow-up), the aHR was 0·67 (0·59–0·77), suggesting a decreased risk of worsening mental illness with semaglutide use compared with other GLP-1 receptor agonists. The results were similar between women and men for all GLP-1 receptor agonists except liraglutide, for which a decreased risk of worsening mental illness was observed for women (aHR 0·78 [0·70–0·87]) but not for men (0·95 [0·83–1·09]; appendix p 9). The

results stratified by type of index episode (depression, anxiety disorder, or both) are shown in the appendix (p 10).

When the analysis was restricted to periods after semaglutide received its European Marketing Approval in 2018, semaglutide continued to be associated with a lower risk of worsening mental illness (aHR 0·62 [95% CI 0·54–0·71]; appendix p 11).

Regarding the secondary outcomes, comprising analysis of the primary outcome by diagnostic subcategories, semaglutide was associated with reduced risk of worsening depression (aHR 0·56 [95% CI 0·44–0·71) and of a worsening anxiety disorder (0·62 [0·52–0·73]) whereas liraglutide was linked only with lower risk of worsening depression (0·74 [0·64–0·87]; figure 2; appendix pp 3–4). For additional subcategories of the primary outcome, semaglutide was associated with decreased risk of worsening substance use disorder (0·53 [0·35–0·80]), whereas liraglutide was not (figure 3). Any GLP-1 receptor agonist use (at the group level) was associated with a decreased risk of self-harm (0·56 [0·34–0·92]; figure 3). There were 171 deaths by suicide during the study period (one of which occurred during GLP-1 receptor agonist use) but these deaths contributed only 0·2% to the main outcome.

When the main outcome was restricted to inpatient events, semaglutide was linked with a reduced risk of psychiatric or self-harm hospitalisation (aHR 0·72 [95% CI 0·59–0·89]; figure 4; appendix pp 3–4). Restricting the outcome to sick leave, semaglutide (0·55 [0·47–0·64]) and liraglutide (0·88 [0·80–0·97]) were associated with a lower risk of sick leave due to any psychiatric reason or self-harm.

After omitting the first 30 days or first 60 days from exposure and non-exposure periods, to remove possible carryover effects from GLP-1 receptor agonist exposures to non-exposure periods, the aHRs remained similar to those from the main analysis. For semaglutide, the aHR was 0·56 (95% CI 0·50–0·64) after omission of 30 days and 0·56 (0·49–0·63) after omission of 60 days. For liraglutide, the aHR was 0·86 (0·79–0·94) after omission of 30 days and 0·87 (0·79–0·95) after omission of 60 days.

The most common second-line antidiabetics identified in the study cohort were empagliflozin (11 809 [12·4%] of 95 490 individuals), followed by semaglutide (10 967 [11·5%]), liraglutide (9872 [10·3%]), sitagliptin (9243 [9·7%]), and dapagliflozin (4296 [4·5%]). Characteristics of individuals who used semaglutide and empagliflozin are shown in the appendix (p 5). Compared with empagliflozin, which was chosen as the main comparator, semaglutide (aHR 0·73 [95% CI 0·62–0·87]) was associated with a decreased risk of worsening mental illness, whereas dapagliflozin (1·24 [1·02–1·52]) and sitagliptin (1·49 [1·31–1·68]) were associated with an increased

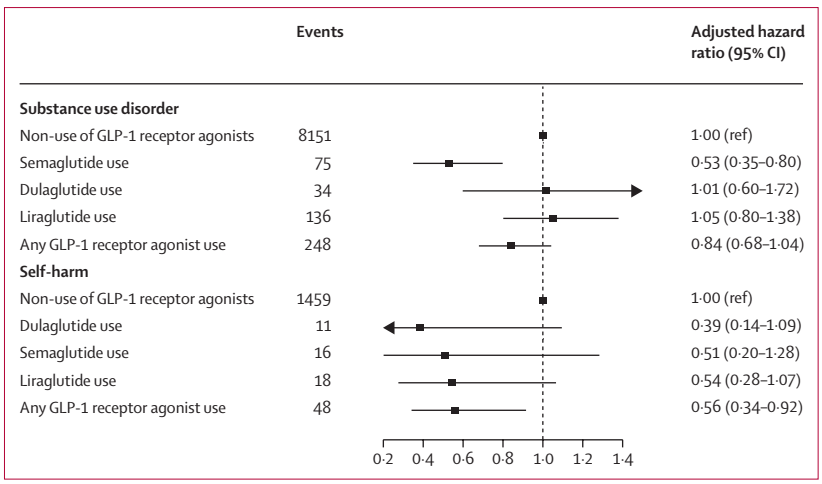

Figure 3: **Risk of substance use disorder and self-harm outcomes associated with GLP-1 receptor agonist use compared with non-use periods in a within-individual model**
Numbers of individuals and person-years are the same as in figure 1.

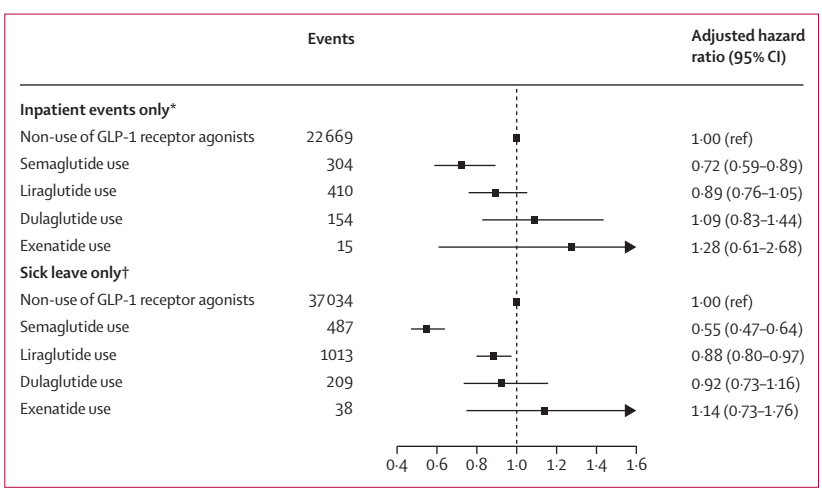

Figure 4: **Individual elements of the main outcome (inpatient events and sick leave) associated with GLP-1 receptor agonist use compared with non-use periods in a within-individual model**
Numbers of individuals and person-years are the same as in figure 1. *Psychiatric hospitalisations and hospitalisations due to self-harm. †Full-time or part-time sickness absence for more than 14 days for any psychiatric reason.

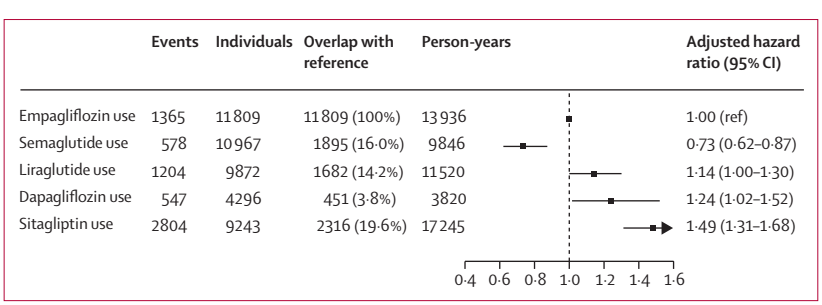

Figure 5: **Risk of worsening mental illness associated with use of commonly used specific second-line antidiabetics (semaglutide, liraglutide, dapagliflozin, and sitagliptin) compared with empagliflozin in a within-individual model**

risk (figure 5; appendix pp 3–4). The results for semaglutide were similar when the reference category was changed to sitagliptin or dapagliflozin (appendix p 11).

In a post-hoc subanalysis, among those using an antidiabetic medication other than GLP-1 receptor agonists at cohort entry (n=88 075), the results remained similar for the main outcome (aHR 0·56 [95% CI 0·49–0·64] for semaglutide and 0·83 [0·76–0·91] for liraglutide; appendix p 12).

Discussion

We found that semaglutide and, to a lesser extent, liraglutide were associated with significantly lower risk of worsening mental illness—defined as a combination of hospitalisation due to mental disorder or self-harm, sick leave for psychiatric reasons, or suicide—in people using antidiabetic medications, compared with time periods when GLP-1 receptor agonists were not used. When compared with time periods in which other second-line antidiabetic medications were used, semaglutide and liraglutide use periods were also associated with a significantly better outcome.

GLP-1 receptor agonist use generally was associated with a reduced risk of self-harm and substance use disorder in this sample.

Anxiety and depression often co-occur in clinical practice, and people with diabetes have an elevated likelihood of developing these disorders,[3,4] as impaired glycaemic control can be exacerbated by comfort eating and intermittent antidiabetic medication adherence, reinforcing low mood and poor self-worth. De Giorgi and colleagues reviewed[1] several studies investigating GLP-1 receptor agonists across mood and anxiety disorders, and concluded that there was mixed evidence, with beneficial, harmful, or no effects on depressive symptoms and suicidal behaviour being reported. Other recent studies and reviews[18–23] have also found mixed evidence, but the consensus appears to be that GLP-1 receptor agonists are not usually associated with adverse psychiatric outcomes once confounding is controlled for.

We found a 42% lower risk for worsening mental illness in people using semaglutide, and an 18% decreased risk in those using liraglutide, but not in those using exenatide or dulaglutide. Thus, this association does not appear to reflect a GLP-1 receptor agonist class effect and cannot simply be attributable to better medication adherence through weekly injectables, unless the reduced risk is entirely due to differential weight loss between GLP-1 receptor agonist agents. We note that a related paper on a population of US Veterans found reductions in alcohol misuse associated with GLP-1 receptor agonists, which were not related to baseline BMI.[24]

Semaglutide was significantly better than any other GLP-1 receptor agonist regarding our main outcome of worsening mental illness and was the only GLP-1 receptor agonist to be significantly associated with benefits for our secondary anxiety and depression outcomes, whereas liraglutide was associated with only a beneficial depression-related outcome. This is consistent with findings that semaglutide can produce greater weight loss than liraglutide[25] and a meta-analysis indicating that semaglutide is superior to liraglutide, dulaglutide, and exenatide in terms of glycaemic control and weight loss.[26] However, our study does not provide evidence that weight loss directly caused improved mental health, and the relationship between the medications, weight loss, and mental health is likely to be complex.

In the main analysis, periods of GLP-1 receptor agonist use were compared with periods of GLP-1 receptor agonist non-use in the same individuals with adjustment for concomitant medication use, including antidepressants and other medications for mood disorders, as well as other antidiabetic medications. We also tested whether possible mood effects were related to the phase or severity of diabetes, comparing semaglutide and liraglutide directly with other second-line antidiabetics for which adequate statistical power was available, namely sitagliptin, dapagliflozin, and empagliflozin.

Of the other antidiabetic medications studied, empagliflozin was linked with a lower risk of worsening mental illness compared with sitagliptin or dapagliflozin in this cohort and was chosen as the main comparator drug. Semaglutide was associated with a significantly lower risk of worsening mental illness when compared directly with empagliflozin. In a further post-hoc analysis excluding people who entered the cohort using a GLP-1 receptor agonist (who might have been using the medication for obesity and not for diabetes), we found the same results as in the main analysis. Thus, the findings cannot be linked simply with the severity or phase of the underlying diabetes.

The temporal order of treatments (use *vs* non-use of GLP-1 receptor agonists for our main exposure) was adjusted for in the analysis; however, to ensure no bias in a sequence in which an individual first used GLP-1 receptor agonists and then experienced weight rebound after discontinuation of the GLP-1 receptor agonist, we conducted a post-hoc subanalysis among individuals who were using other antidiabetic medications upon cohort entry. As these results did not vary compared with the main analysis, there is no reason to believe that the observed effect would be skewed by the sequence of exposure versus non-exposure.

From an employers' and policy makers' perspective, the reduction in sick leave from work associated with semaglutide and liraglutide use might be of particular interest. Depression and anxiety disorders are common causes for sickness absences from work in many countries[8] and can lead to long-term incapacity.

Our results also suggest that GLP-1 receptor agonists are significantly associated with a reduction in self-harm when analysed as a group, although a lack of statistical power precluded comparison between individual GLP-1 receptor agonists. This diminished risk of self-harm with GLP-1 receptor agonist use is corroborated by other work[10,11,27–33] and counters earlier concerns about a potential increased risk of suicidal behaviour linked to GLP-1 receptor agonist use.[13] A large observational study[27] also noted that semaglutide diminished the risk of suicidal thinking, and two long case-control studies[28,29] with large samples of people with diabetes observed no association between GLP-1 receptor agonist use and incident depression. A recent meta-review[11] concluded that there was no evidence for GLP-1 receptor agonist treatment leading to depression and self-harm, and the authors recommended that future studies of GLP-1 receptor agonists routinely collect data on depression.

Additionally, the results presented here are consistent with our previous work[12] that showed reduced hospitalisation due to substance use disorder in people using semaglutide. The current study, however, suggests that semaglutide has a psychiatric effect beyond substance use, as our results remained significant when substance use disorder was excluded and when outcome was solely restricted to depression and anxiety.

There is a theoretical basis[34,35] for GLP-1 receptor agonists improving symptoms of anxiety and depression through the mesolimbic and frontocortical serotonergic and dopaminergic pathways, possibly through increased insulin production affecting neurotransmission. GLP-1 hormone might reduce neuroinflammation through decreased oxidative stress and reduced production of reactive oxygen species and inflammatory cytokines.[35] Activation of cyclic AMP and its receptor by GLP-1 receptor agonists can promote the phosphorylation of cAMP response element-binding protein, leading to gene expression involving neuronal survival and regeneration. GLP-1 receptor stimulation has also been associated[35] with neuroprotective and neurotrophic properties in animal studies, and rat hippocampal neurons treated with GLP-1 receptor agonists were more resistant to glutamate excitotoxicity, leading to enhanced neural growth and differentiation. Thus, any psychiatric effects of GLP-1 receptor agonists could be due to a direct effect on brain function as well as weight loss,[1] although gender might mediate these complex interactions.[36]

The study has several limitations. First, these results are generalisable only to health-care systems similar to that in Sweden, where health and social care are provided free at the point of service to all residents, with minimal out-of-pocket costs. The cost of GLP-1 receptor agonists can be an obstacle to access in private health-care systems for people who would most benefit from these medications until cheaper generic GLP-1 receptor agonist medications become available. It is possible that the costs of GLP-1 receptor agonists played some role in this study, although all second-line antidiabetics are associated with relatively similar costs and people using GLP-1 receptor agonists were not overtly socioeconomically different from the whole sample (table).

The main limitation of this work is that causality cannot be attributed in an observational study, although the robust associations found between individual antidiabetic medications provide a basis for future randomised controlled trials. No individual data on symptom severity or parameters such as weight change, HbA_{1c}, or BMI are available in the national registers used. We reported the median durations of semaglutide and liraglutide use, but these periods could be affected by drug shortages during the observation period and should not be considered direct measures of adherence. Due to market-related drug shortages, or a lack of statistical power, and certain medications (liraglutide) having only one strength, as well as the fixed administration dosing interval, comparative dose–response analyses were not feasible.

Statistical power was low for our results for dulaglutide and exenatide. Residual confounding, particularly by indication, might occur, as in all observational studies, despite the within-individual comparisons and adjustment for the temporal order of exposures and concomitant medication use, covering both the severity of diabetes and the psychiatric condition. Finally, our study period covered the COVID-19 pandemic and it possible that COVID-19 affected our results; Swedish data on the effect of the COVID-19 pandemic period noted a lower suicide rate and no major changes in antidepressant use or sick leave.[37,38]

Using national observational data collected over a 14-year period, we have shown that semaglutide and, to a lesser extent, liraglutide were associated with a significantly lower risk of worsening mental illness in people using antidiabetic medications, whereas exenatide and dulaglutide were not. With regard to secondary outcomes, GLP-1 receptor agonist use was associated with a lower risk of self-harm, and semaglutide use was associated with a decreased risk of worsening depression, anxiety, and substance use disorder. Our findings suggest that a randomised controlled trial of GLP-1 receptor agonist use in people with diabetes and depression, anxiety, or both would be worthwhile.

Contributors

Study concept: ML, HT, and JT. Analytical design: HT and AT. Data analysis: HT and AT. Access to the aggregated data and results data: all authors. Access to individual-level data: HT, AT, and EM-R. Verification of data: HT and AT. First draft: MT and HT. Interpretation of results: all authors. Decision to submit the manuscript: all authors.

Declaration of interests

HT, EM-R, and JT have participated in research projects funded by grants from Janssen to their employing institution. HT reports personal

fees from Gedeon Richter, Janssen, Lundbeck and Otsuka; and has been a consultant or advisor to or has received honoraria from Healthcare Global Village, HLS Therapeutics, Janssen-Cilag, Lundbeck, Orion, Otsuka, Teva, and WebMD Global. ML has received honoraria from Lundbeck, Otsuka Pharma, Janssen, Johnson & Johnson, Orion Pharma, and Recordati. MT declares no competing interests.

Data sharing

The Swedish data used in this study cannot be made publicly available due to privacy regulations. According to the General Data Protection Regulation, the Swedish law SFS 2018:218, the Swedish Data Protection Act, the Swedish Ethical Review Act, and the Public Access to Information and Secrecy Act, these types of sensitive data can only be made available for specific purposes, including research, that meets the criteria for access to this sort of sensitive and confidential data as determined by a legal review. Readers can contact EM-R (ellenor.mittendorfer-rutz@ki.se) regarding the data. Researchers can apply for access to these data from the register holders: the National Board of Health and Welfare (National Patient Register, Prescribed Drug Register and the Cause of Death Register), Statistics Sweden (sociodemographic data in the LISA Register), and the Swedish Social Insurance Agency (data on sickness absence and disability pension in the MiDAS Register).

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