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Association of semaglutide with risk of suicidal ideation in a real-world cohort

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Abstract

Concerns over reports of suicidal ideation associated with semaglutide treatment, a glucagon-like peptide 1 receptor (GLP1R) agonist medication for type 2 diabetes (T2DM) and obesity, has led to investigations by European regulatory agencies. In this retrospective cohort study of electronic health records from the TriNetX Analytics Network, we aimed to assess the associations of semaglutide with suicidal ideation compared to non-GLP1R agonist anti-obesity or anti-diabetes

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Author contributions

R.X. conceived the study. R.X. and N.D.V. designed the study. W.W. performed the data analysis and created the tables and figures. R.X. and N.D.V. interpreted the results and drafted the paper. N.A.B., P.B.D. and D.C.K. critically contributed to study design, result interpretation and paper preparation. R.X. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-023-02672-2.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Code availability

All the statistical analyses in this study, including propensity score matching and Kaplan–Meier survival analyses were conducted using the TriNetX platform with its built-in functions. The data and code needed to reproduce the analyses can be accessed at https://github.com/bill-pipi/semaglutide_suicide.

Competing interests

The authors declare no competing interests.

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medications. The hazard ratios (HRs) and 95% confidence intervals (CIs) of incident and recurrent suicidal ideation were calculated for the 6-month follow-up by comparing propensity score-matched patient groups. The study population included 240,618 patients with overweight or obesity who were prescribed semaglutide or non-GLP1R agonist anti-obesity medications, with the findings replicated in 1,589,855 patients with T2DM. In patients with overweight or obesity (mean age 50.1 years, 72.6% female), semaglutide compared with non-GLP1R agonist anti-obesity medications was associated with lower risk for incident (HR = 0.27, 95% CI = 0.200.32–0.600.36) and recurrent (HR = 0.44, 95% CI = 0.32–0.60) suicidal ideation, consistent across sex, age and ethnicity stratification. Similar findings were replicated in patients with T2DM (mean age 57.5 years, 49.2% female). Our findings do not support higher risks of suicidal ideation with semaglutide compared with non-GLP1R agonist anti-obesity or anti-diabetes medications.

Suicide is a serious and preventable public health concern with 759,028 people reported worldwide to have died from suicide in 2019 (ref. 1). Suicide is among the top 10 leading causes of death and the fourth among people aged 15–29 years[2]. Suicide death rates vary according to demographics, with males having 2–3 times higher rates than females and people older than 85 years having some of the highest rates globally[3]. In the United States, provisional data from the Centers for Disease Control and Prevention calculated that in 2022 over 49,449 individuals died by suicide, with suicide rates among the highest in people aged between 25 and 34 years of age and over 75 years of age[4].

Thus, a concern for the U.S. Food and Drug Administration (FDA) and other regulatory agencies that approve medications for human use is to minimize the risks that these medications increase suicidal ideation. Although preapproval trials are required to show a lack of suicidal ideation, their predictive accuracy for safety is constrained by the relatively limited number of patients included[5]. To address this, regulatory agencies have established several post-marketing surveillance methods that can lead to ‘black box’ labels for the highest safety-related warning or potential drug removal. However, the sensitivity and accuracy of these methods have been questioned[6]. A study that used the MarketScan database to review 922 drugs prescribed between 2003 and 2014 identified ten drugs associated with increased risk of suicidal ideations and 44 drugs associated with decreased risk, including many that required a ‘black box’ label by the FDA warning of their association with suicide rates[6].

Reported associations with increased risk for depression and suicide has led to post-marketing removal of the weight-loss drug rimonabat by the European Medicines Agency (EMA)[7]. Another example is Qnexa (Vivus) containing two active ingredients, phentermine and topiramate, which despite demonstrating more than 9% body weight loss, was rejected by the FDA partly because of concerns regarding the potential risk of increased suicidal ideation[7].

Glucagon-like peptide 1 receptor (GLP1R) agonists initially developed as anti-diabetes medications are highly effective for weight loss[8,9]. Currently, both liraglutide and semaglutide are approved by the FDA and the EMA for weight loss[10,11]. In July 2023, the EMA[12] and the Medicines and Healthcare Products Regulatory Agency in the United Kingdom initiated an investigation of Novo Nordisk’s diabetes drug Ozempic (semaglutide)

and weight-loss treatment Wegovy (semaglutide) after reported cases of suicidal ideation associated with their use[12]. In the United States, the FDA through its Event Reporting System also received reports of suicidal ideation associated with semaglutide[13], although these reports have not been verified. Suicidal ideation has been linked to other weight-loss drugs[14] and the clinical trial that led to the FDA's approval of semaglutide excluded participants with a recent history of suicidal ideation[15]. Instructions for Wegovy include recommended monitoring for suicidal ideation[16]. However, the association of semaglutide with suicidal ideation compared with non-GLP1R agonist medications has not been investigated.

In this study, we used a large electronic health record (EHR) database to conduct a nationwide retrospective cohort study to assess the association of semaglutide with the incidence and recurrence of suicidal ideation compared with non-GLP1R agonist anti-obesity medications in individuals with overweight or obesity. We replicated the same analyses in a separate cohort of patients with type 2 diabetes mellitus (T2DM) by comparing semaglutide with non-GLP1R agonist anti-diabetes medications.

Results

Suicidal ideation in patients with overweight or obesity

For the analysis of incident suicidal ideation in patients with overweight or obesity, the study population included 232,771 patients who had no previous history of suicidal ideation. The semaglutide group compared with the non-GLP1R agonist anti-obesity medication (bupropion, naltrexone, orlistat, topiramate, phentermine, setmelanotide) group was older, included more males, had a lower prevalence of adverse socioeconomic determinants, mental health disorders, substance use disorders and higher prevalence of T2DM. After propensity score matching, the two groups (52,783 in each group, mean age 50.1 years, 72.6% female, 7.4% Hispanic, 16.0% Black) were balanced (Table 1).

The matched semaglutide and non-GLP1R agonist anti-obesity medication groups were followed during the 6-month time window after the index event (first prescription of semaglutide versus non-GLP1R agonist anti-obesity medications occurred from June 2021 through to December 2022). The mean follow-up time was 160.5 ± 18.4 days for the semaglutide group and 150.2 ± 26.8 days for the non-GLP1R agonist anti-obesity medication group. The semaglutide group had a significantly lower risk for incident suicidal ideation than the matched non-GLP1R agonist anti-obesity medication group (0.11% versus 0.43%; hazard ratio (HR) = 0.27, 95% confidence interval (CI) = 0.20–0.36). Consistent lower risks were observed in patients stratified according to sex, age group, ethnicity and ethnic grouping (Fig. 1). Among 52,783 patients in the semaglutide group, no patient reported suicide attempts during the 6-month follow-up after semaglutide prescription, whereas 14 of 52,783 patients reported suicidal attempts in the matched non-GLP1R agonist anti-obesity medication group during the 6-month follow-up after medication prescription ($P < 0.001$)

For the analysis of recurrent suicidal ideation in patients with overweight or obesity, the study population included 7,847 patients who had a previous history of suicidal ideation.

The semaglutide group compared to the non-GLP1R agonist anti-obesity medication group was older, included more females, had a lower prevalence of adverse socioeconomic determinants of health, substance use disorders, suicide attempts and intentional self-harm, and higher prevalence of T2DM, cancer and chronic pain. After propensity score matching, the two groups (865 in each group, mean age 44.4 years, 72.1% female, 6.8% Hispanic, 13.8% Black) were balanced (Extended Data Table 1).

The mean follow-up time for the study population with overweight or obesity and a previous history of suicidal ideations was 160.4 ± 18.2 days for the semaglutide group and 161.4 ± 17.7 days for the non-GLP1R agonist anti-obesity medication group. The semaglutide group was associated with a significantly lower risk for recurrent experience of suicidal ideation (6.5% versus 14.1%; HR = 0.44, 95% CI = 0.32–0.60) and had lower rates of medication prescriptions related to the treatment for suicidal ideation compared to the matched non-GLP1R agonist anti-obesity medication group (69.3% versus 96.6%, HR = 0.28, 95% CI = 0.25–0.32), which was consistent with patient subgroups stratified according to sex and age (Fig. 2). Stratification according to older adults, ethnic grouping and ethnicity was not performed because of limited sample sizes. The number of patients who had suicide attempt during the 6-month follow-up in both groups was between 1 and 9, but the actual number was not reported because of privacy concerns.

Suicidal ideation in patients with T2DM

For the analysis of incident suicidal ideation in patients with T2DM, the study population consisted of 1,572,885 patients with no previous history of suicidal ideation. The semaglutide group compared to the non-GLP1R agonist anti-diabetes medication group (insulin, metformin, sulfonylureas, alpha glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium/glucose co-transporter 2 (SGLT2) inhibitors) was younger, included fewer individuals of Hispanic ethnicity, had a higher prevalence of overweight and obesity, cancer, chronic pain and mental disorders, and higher prevalence of previous non-GLP1R agonist anti-diabetes medication prescriptions. After propensity score matching, the two groups (27,726 in each group, mean age 57.5 years, 49.2% female, 5.8% Hispanic, 15.4% Black) were balanced (Table 2).

The mean follow-up time for patients with T2DM and no previous history of suicidal ideation was 172.9 ± 7.8 days for the semaglutide group and 167.2 ± 13.0 days for the non-GLP1R agonist anti-diabetes medication group. The semaglutide group had a significantly lower risk for incident suicidal ideation than the matched non-GLP1R agonist anti-diabetes medication group (0.13% versus 0.36%; HR = 0.36, 95% CI = 0.25–0.53). Consistent lower risks were seen in patients stratified according to sex, age subgroup and ethnic grouping (Fig. 3). The number of patients who had a suicide attempt during the 6-month follow-up in both groups was between 1 and 9, but the actual number was not reported because of privacy concerns.

For the analysis of recurrent suicidal ideation in patients with T2DM, the study population consisted of 16,970 patients with T2DM who had a previous history of suicidal ideation. The semaglutide group compared to the non-GLP1R agonist anti-diabetes medication group had a similar age, included more females and White individuals, had a higher prevalence

of obesity, cancer, chronic pain, mental, behavioral and sleep disorders, a previous history of suicide attempts and intentional self-harm, lower prevalence of substance use disorders and higher prevalence of previous prescriptions of non-GLP1R agonist anti-diabetes medications. After propensity score matching, the two groups (251 in each group, mean age 50.0 years, 62.0% females, 8.4% Hispanic, 11.6% Black) were balanced (Extended Data Table 2).

The mean follow-up time for patients with T2DM and a previous history of suicidal ideation was 165.9 ± 14.1 days for the semaglutide group and 144.6 ± 31.6 days for the non-GLP1R agonist anti-diabetes medication group. The semaglutide group was associated with a significantly lower risk for recurrent suicidal ideation compared to the matched non-GLP1R agonist anti-diabetes medication group (10.0% versus 17.9%; HR = 0.51, 95% CI = 0.31–0.83). Consistent lower risk was seen in patients stratified according to sex and age group (Extended Data Fig. 1). The semaglutide group had lower medication prescriptions related to suicidal ideation treatment compared to the matched non-GLP1R agonist anti-diabetes medication group (69.7% versus 84.1%, HR = 0.55, 95% CI = 0.45–0.67), which was consistent in patients stratified according to sex and age subgroup (Extended Data Fig. 1). The number of patients who had a suicide attempt during the 6-month follow-up in both groups was between 1 and 9, but the actual number was not reported because of privacy concerns.

We then examined the association of semaglutide prescription with both incident and recurrent suicidal ideation in patients with T2DM for longer follow-ups (1, 2 and 3 years). Compared with non-GLP1R agonist anti-diabetes medications, semaglutide was associated with a lower risk of incident suicidal ideation at longer follow-ups. Similar associations were observed at the 1-year follow-up (HR = 0.39, 95% CI = 0.28–0.53) compared to the 6-month follow-up. At the 3-year follow-up (mean 804.7 ± 156.6 and 859.7 ± 181.0 follow-up days for the semaglutide group and non-GLP1R agonist anti-diabetes medication group, respectively), the associations were attenuated but remained significant, with CIs overlapping with those for the 6-month follow-up (HR = 0.58, 95% CI = 0.49–0.72). The association for the 2-year follow-up was similar to that for the 3-year follow-up (HR = 0.53, 95% CI = 0.41–0.67). The associations of semaglutide with recurrent suicidal ideation at the 2-and 3-year follow-ups (mean 769.5 ± 213.5 and 683.6 ± 279.7 follow-up days for the semaglutide group and non-GLP1R agonist anti-diabetes medication group, respectively) were similar to that at the 6-month follow-up (Fig. 4).

Discussion

Contrary to reports of increases in suicidal ideation with semaglutide, our analyses revealed a lower risk for both incidence and recurrence of suicidal ideation in patients prescribed semaglutide compared with non-GLP1R agonist anti-obesity and anti-diabetes medications. We performed analyses in two separate groups involving patients with overweight and obesity, and in patients with T2DM, from two nonoverlapping periods (from June 2021 through to December 2022 for patients with overweight or obesity and from December 2017 through to May 2021 for patients with T2DM). The characteristics of the group with T2DM (mean age 57.5 years, 49.2% female, 5.8% Hispanic, 15.4% Black) were different

from those of the patients in the group with overweight or obesity (mean age 50.1 years, 72.6% female, 7.4% Hispanic, 16.0% Black); however, the semaglutide-associated lower risk of incident and recurrent suicidal ideation compared to non-GLP1R agonist anti-obesity or anti-diabetes medications were similar. Thus, our results do not support the concerns of increased suicidal risk associated with semaglutide raised by the EMA and Medicines and Healthcare Products Regulatory Agency in the United Kingdom[12]. This highlights the need for a more detailed evaluation of the previously reported cases.

The association between obesity and suicidality is not clear. A recent systematic review reported that while six of eight studies reported a lower risk for suicide in individuals with obesity than those without, one study reported increased risk while another study did not report a relationship[17]. This same systematic review reported that for suicidal ideation and suicide attempts, the risk differed according to sex such that females with obesity had a higher risk than males with obesity. Studies on obesity treatments reported an increased risk of suicidal ideation and suicide attempts, particularly after bariatric surgery[18,19]; one study reported an association for some anti-obesity medications[20]. Mental health disorders, including depression and suicidal ideation, are more prevalent in individuals with T2DM than in the general population[21], emphasizing the importance of disease management through informed anti-diabetes medication choices.

Our study has several limitations: this was a retrospective observational study, so no causal inferences can be drawn. Furthermore, patients in the TriNetX database (https://trinetx.com/) represented those who had medical encounters with healthcare systems contributing to the TriNetX platform. Even though this platform includes over 100 million patients in the United States, it does not necessarily represent the entire US population. Therefore, results from the TriNetX platform need to be validated in other populations.

There are limitations inherent to observational studies and studies based on patient EHRs, including overdiagnosis, misdiagnosis and underdiagnosis, unmeasured or uncontrolled confounders, self-selection and reverse causality. For example, when initiating semaglutide, some healthcare providers are more closely involved in the early stages to ensure proper injection techniques. It is possible that the increased interactions might have led to better outcomes, thus influencing the rates of suicidal ideation. Alternatively, they might have strengthened trust and facilitated the willingness of a patient to report suicidal ideation. Future controlled trials are necessary to assess any causal relationships between semaglutide with suicidal ideation.

In our study, the follow-up time for the main analyses was 6 months. Semaglutide was approved as a weight management medication in June 2021. The study period for the study population of patients with overweight or obesity ran from 1 June 2021 through to 31 December 2022; this provided us with large-enough cohort and a sufficient sample size, while allowing us to have a 6-month follow-up for all patients for data analyses on 1 September 2023. However, a major issue with short follow-up time windows is reverse causality[22] whereby undiagnosed suicidal ideation and related medical conditions might have impacted the choice of semaglutide versus non-GLP1R agonist anti-obesity and anti-diabetes medications. In the study population with T2DM in whom we conducted a longer

follow-up to 3 years, we observed consistently lower risks in both incident and recurrent suicidal ideation. Although this longer time frame might have mitigated the likelihood of reverse causality, biases may have remained; future studies should evaluate longer-term associations of semaglutide with suicidal ideation in the study population with overweight or obesity and in patients with T2DM.

EHR data had limited information on semaglutide brand names and dosage information: 57.1% had unknown dosage and 70.8% had unknown brand name information. Because of limited sample sizes at the time of our study, we could not directly compare dosage effects and the association of semaglutide with suicidal ideation in the same study population. The higher-dose format of semaglutide as Wegovy was approved for weight management (recommended dose of 2.4 mg administered subcutaneously once a week); the lower-dose format of semaglutide as Ozempic was approved for the treatment of T2DM (recommended dose for the subcutaneous formulation = 0.5–1 mg once a week). We observed stronger associations of semaglutide with suicidal ideation in the population with overweight or obesity than in the population with T2DM, which could suggest a potential dose effect. However, the characteristics of the study populations, comparators and study periods were different.

We were unable to assess patients' medication adherence based on their EHRs. Patients may discontinue using the drug for reasons such as financial burden, drug side effects or lack of efficacy. One study showed that adherence with semaglutide was greater than other GLP1R agonists in patients with T2DM[23]. However, adherence to semaglutide compared to non-GLP1R agonist anti-diabetes or anti-obesity medications is unknown. In our study, both study populations included patients who had recent medical encounters when the diagnosis of obesity or overweight, or T2DM, was made and were subsequently prescribed semaglutide or non-GLP1R agonist anti-obesity or anti-diabetes medications, suggesting that patients with active obesity or overweight or T2DM needed medical attention and treatment. However, we could not directly control for patient adherence to medications in this study. In addition, we could not directly control for disease severity and how well medical conditions were managed, including diabetes duration, glycemic control, body mass index and lipid profile, which could have confounded the findings.

Finally, this study was focused on suicidal ideation as an analysis outcome. While we also assessed the associations of semaglutide with suicide attempt, sample sizes were too small for statistical evaluation. Because suicide attempt is critically different from suicidal ideation[24], future studies should continue to evaluate the associations between semaglutide and suicide attempt and non-suicidal self-injury.

In conclusion, our analyses do not support concerns of increased risk of suicidal ideation with semaglutide and instead show a lower risk association of semaglutide with both incident and recurrent suicidal ideation compared to non-GLP1R agonist anti-obesity and anti-diabetes medications. Further studies should evaluate the association of semaglutide and other GLP1R agonist medications with the incidence and recurrence of suicidality in other at-risk populations.

Methods

Data

The data used in this study were collected and analyzed on 1 September 2023 within the TriNetX Analytics platform based on the Research US Collaborative Network. We used the TriNetX platform to access the aggregated, de-identified EHRs of 100.8 million patients from 59 healthcare organizations in the United States across 50 states, covering diverse geographical regions, age, ethnicity, income and insurance groups, and clinical setting. The geographical distribution of patients from the TriNetX platform is 25% in the Northeast, 17% in the Midwest, 41% in the South and 12% in the West, with 5% unknown.

TriNetX is a platform that de-identifies and aggregates EHR data from contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations across all 50 states in the United States. TriNetX Analytics provides Web-based and secure access to patient EHR data from hospitals, primary care and specialty treatment providers, covering diverse geographical locations, age groups, ethnic groups, income levels and insurance types, including several commercial insurances, governmental insurance (Medicare and Medicaid), self-pay and uninsured, worker compensation insurance, and military and Veterans Affairs insurance, among others.

Self-reported sex (female, male), ethnic grouping and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: (1) race: Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other, White, unknown; and (2) ethnicity: Hispanic or Latino, non-Hispanic or Latino, unknown ethnicity.

TriNetX carries out an intensive data preprocessing stage to minimize missing values. TriNetX maps the data to a consistent clinical data model with a consistent semantic meaning so that the data can be queried consistently regardless of the underlying data source(s). All covariates are either binary, categorical, which is expanded to a set of binary columns, or continuous but essentially guaranteed to exist. Age is guaranteed to exist. Missing sex values are represented using ‘unknown sex’. The missing data for ethnic grouping and ethnicity are presented as ‘unknown race’ or ‘unknown ethnicity’. For other variables, including medical conditions, procedures, laboratory tests and socioeconomic determinant health, the value is either present or absent, so ‘missing’ is not pertinent.

Ethics statement

TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX platform in aggregate form, or any patient-level data provided in a dataset generated by the TriNetX platform, only contains de-identified data as per the de-identification standard defined in Section 164.514(a) of the HIPAA Privacy Rule. TriNetX built-in analytical functions (for example, incidence, prevalence, outcomes analysis, survival analysis, propensity score matching) allow for patient-level analyses, while only reporting population-level data. The MetroHealth System

institutional review board-determined research using de-identified aggregated data on the TriNetX platform, in the ways described in this article, is not human subject research. The TriNetX platform has been successfully used in retrospective cohort studies[25–35], including evaluating the risks and benefits of FDA-approved medications in real-world populations[33,36–39]. This study fully complies with the STrengthening the Reporting of OBservational studies in Epidemiology statement.

Statistical analysis

Study population with overweight or obesity.—To assess the incidence of suicidal ideation in patients with overweight or obesity, the study population consisted of 232,771 patients with overweight or obesity who were prescribed semaglutide (Wegovy) or non-GLP1R agonist anti-obesity medications (bupropion, naltrexone, orlistat, topiramate, phentermine, setmelanotide)[40] from 1 June 2021 through to 31 December 2022 and who had medical encounters for the diagnosis of overweight or obesity within 1 month before being prescribed anti-obesity medication, had no history of suicidal ideation before being prescribed the medication and were never prescribed other GLP1R agonist medications. The start date of June 2021 was chosen because semaglutide was approved in the United States for weight management in June 2021. The ending date of 31 December 2022 was chosen to allow for a 6-month follow-up by the time of data collection and analysis in September 2023. This study population was then divided into two groups: (1) a semaglutide group, 67,804 patients prescribed semaglutide; and (2) a non-GLP1R agonist anti-obesity medication group, 164,967 patients prescribed non-GLP1R agonist anti-obesity medications but not semaglutide.

To assess the recurrence of suicidal ideation in patients with overweight or obesity, the study population consisted of 7,847 patients with overweight or obesity who were prescribed semaglutide (Wegovy) or non-GLP1R agonist anti-obesity medications from 1 June 2021 through to 31 December 2022, had medical encounters for overweight or obesity diagnosis within 1 month before being prescribed the medication, had a history of suicidal ideation before being prescribed anti-obesity medication and were never prescribed other GLP1R agonist medications. This study population was divided into two groups: (1) a semaglutide group, 893 patients prescribed semaglutide; and (2) a non-GLP1R agonist anti-obesity medication group, 6,954 patients prescribed non-GLP1R agonist anti-obesity medications but not semaglutide.

Study population with T2DM.—To assess the incidence of suicidal ideation in patients with T2DM, the study population consisted of 1,572,885 patients with T2DM who were prescribed semaglutide (Ozempic) or non-GLP1R agonist anti-diabetes medications from 1 December 2017 through to 31 May 2021, had medical encounters for T2DM within 1 month before being prescribed the medication, had no history of suicidal ideation before being prescribed anti-diabetes medication and were never prescribed other GLP1R agonist medications. The status of non-GLP1R agonist anti-diabetes medications was determined according to the ATC code A10 ‘Drugs used in diabetes’ with GLP1R agonists (ATC code A10BJ ‘Glucagon-like peptide-1 (GLP-1) analogues’) excluded. The list of non-GLP1R agonist anti-diabetes medications included insulin (ATC code A10A ‘Insulins and

analogues'), metformin (ATC code A10BA 'Biguanides'), sulfonylureas (ATC code A10BB 'Sulfonylureas'), alpha glucosidase inhibitors (ATC code A10BF 'Alpha glucosidase inhibitors'), thiazolidinediones (ATC code A10BG 'Thiazolidinediones'), DPP-4 inhibitors (ATC code A10BH 'Dipeptidyl peptidase 4 (DPP-4) inhibitors') and SGLT2 inhibitors (ATC code A10BK 'Sodium-glucose co-transporter 2 (SGLT2) inhibitors') (Extended Data Table 3). The study starting date of December 2017 was chosen because semaglutide was approved in the United States as Ozempic for T2DM in December 2017, earlier than its approval for weight management as Wegovy in June 2021. The ending date of May 2021 was chosen to allow us to separately examine the associations of semaglutide with suicidal ideation as Ozempic from those in the study population with overweight or obesity prescribed Wegovy. This study population was divided into two groups: (1) a semaglutide group, 27,282 patients prescribed semaglutide; and (2) a non-GLP1R agonist anti-diabetes medications group, 1,545,603 patients prescribed non-GLP1R agonist anti-diabetes medications but not semaglutide.

To assess the recurrence of suicidal ideation in patients with T2DM, the study population consisted of 16,970 patients with T2DM who were prescribed Ozempic or non-GLP1R agonist anti-diabetes medications from 1 December 2017 through to 31 May 2021, had medical encounters for T2DM within 1 month before being prescribed the medication, had a history of suicidal ideation before being prescribed the medication and were never prescribed other GLP1R agonist medications. This study population was divided into two groups: (1) a semaglutide group, 253 patients prescribed semaglutide; and (2) a non-GLP1R agonist anti-diabetes medication group, 16,717 patients prescribed non-GLP1R agonist anti-diabetes medications but not semaglutide.

For each study population, the semaglutide and the non-GLP1R agonist anti-obesity or anti-diabetes medication groups were propensity score-matched (1:1 using nearest neighbor greedy matching with a caliper of 0.25 times the s.d.) on covariates that are potential risk factors for suicidal ideation[41,42], including demographics (age, sex, ethnic grouping/ethnicity, marriage status); adverse socioeconomic determinants of health (for example, education, unemployment, upbringing, social and psychosocial environment, and housing); lifestyle problems (for example, smoking, gambling and betting, exercise, diet); substance use disorders (for example, alcohol, tobacco or other nicotine products, cannabis, cocaine, stimulants); psychiatric comorbidities (for example, mood disorders, anxiety disorders, psychotic disorders); behavior disorders (for example, eating or sleep disorders); chronic pain, cancers, traumatic brain injury and bariatric surgery; previous medication prescriptions for obesity and T2DM for all groups; previous suicide attempt and intentional self-harm; and pharmacotherapies for suicidal ideation for the groups to evaluate the recurrence of suicidal ideation (Extended Data Table 3).

The outcome–first or recurrent suicidal ideation–that occurred in the 6-month time window after the index event (prescription of semaglutide versus non-GLP1R agonist anti-obesity or anti-diabetes medications) were compared between the matched semaglutide and non-GLP1R agonist anti-obesity or anti-diabetes medication groups. The status of suicidal ideation was based on the presence or absence of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) code R45.851 'Suicidal

ideations' recorded in patient EHRs. For ICD-10 code R45.852 suicidal ideation is diagnosed if a patient expresses thoughts about suicide (fleeting or sustained), including planning how to proceed with a suicide or acting on it but surviving because of failure of the method chosen or because of early discovery. To evaluate the associations of semaglutide with the recurrence of suicidal ideation, an additional outcome—prescription of medication related to suicidal ideation pharmacotherapy (esketamine, ketamine, lithium, antidepressants, antipsychotics, antiepileptics, benzodiazepines and hypnotics)[43]—was examined.

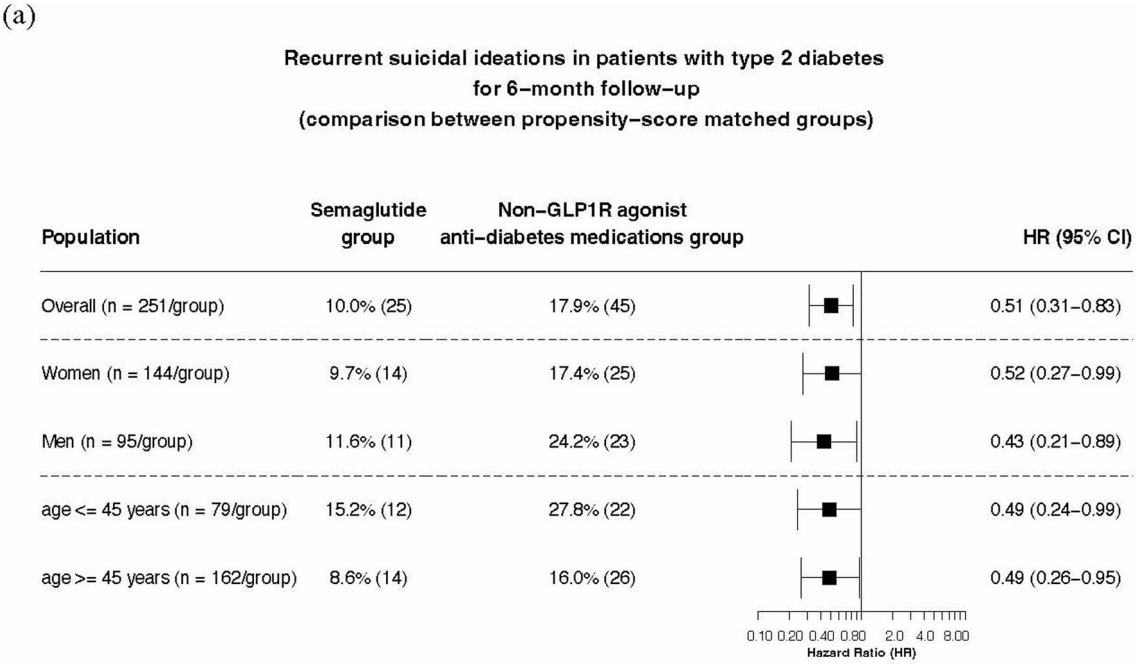
An additional outcome–first experience of suicide attempt (ICD-10 code T14.91 'Suicide attempt')–was examined for the study population with overweight or obesity who had no previous history of suicidal ideations or suicide attempt, but not in other groups because of small sample sizes. Because of privacy concerns, groups of 1–9 cases were rounded up to 10 to protect patient information. For groups other than the study population with overweight or obesity who had no previous history of suicidal ideation or suicide attempt, the number of patients whose outcome was suicide attempt was 10,; this could be any number from 1 to 10.

For the study population with T2DM, the index event was the first prescription of semaglutide versus non-GLP1R agonist anti-diabetes medications, occurring from 1 December 2017 through to 31 May 2021. To examine longer-term associations of semaglutide prescription with suicidal ideation, the outcome, that is, first and recurrent experience of suicidal ideation, in patients with T2DM was further followed for 1, 2 and 3 years starting from the index event.

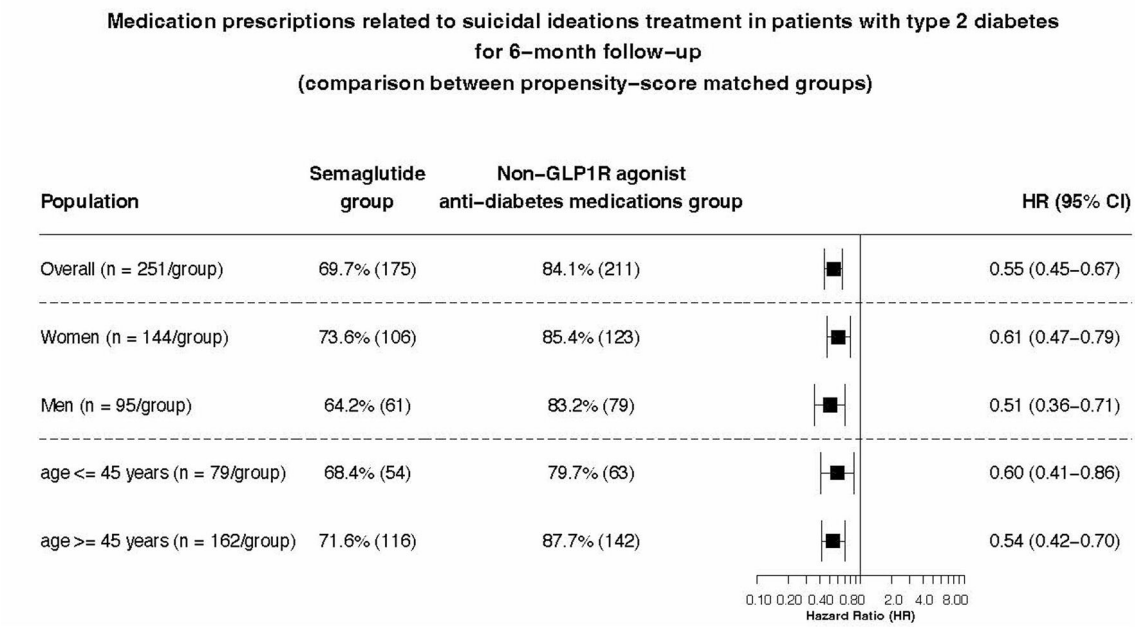
Kaplan–Meier analysis was used to estimate the probability of outcome at daily time intervals with censoring applied. When the last fact (outcomes of interest or other medical encounters) in the patient's record was in the time window for analysis, the patient was censored on the day after the last fact in their record. HRs and 95% CIs were used to describe the relative hazard of the outcomes based on a comparison of time-to-event rates. Separate analyses were performed in patients stratified according to sex (female, male), age subgroups (≤45, 46–64, ≥65 years), ethnic grouping and ethnicity (Black, White, Hispanic). Data were collected and analyzed on 1 September 2023 within the TriNetX Analytics platform.

Extended Data

(a)



(b)



Extended Data Fig. 1|. Comparison of (a) recurrent suicidal ideations and (b) medication prescriptions for suicidal ideations treatments in patients with type 2 diabetes (T2DM) who had a prior history of suicidal ideations between propensity-score matched semaglutide and non-GLP1R agonist anti-diabetes medications groups for 6-month follow-up period.

For each group, overall risk (# of cases) is also shown, where overall risk is defined as the number of patients with outcomes during the 6-month follow-up period/number of patients in the cohort at the beginning of the follow-up time period.

Extended Data Table 1|

Characteristics of the semaglutide and non-GLP1R agonists anti-obesity medications groups for patients with overweight or obesity who had a prior history of suicidal ideations

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	**Non-GLP1R agonists anti-obesity medications**	**SMD**	**Semaglutide**	**Non-GLP1R agonists anti-obesity medications**	**SMD**
Total number	893	6,954		865	865	
Age at index event (years, mean±standard deviation)	44.7 ± 14.1	41.8 ± 15.5	0.20 *	44.3 ± 14.0	44.6 ± 15.7	0.02
Sex (%)						
Female	71.7	67.0	0.10 *	71.7	72.5	0.02
Male	28.3	32.8	0.10 *	28.3	27.3	0.02
Ethnicity (%)						
Hispanic/Latinx	6.9	8.3	0.05	6.7	6.8	0.005
Not Hispanic/Latinx	82.9	82.8	0.003	83.0	80.5	0.07
Unknown	10.2	9.0	0.04	10.3	12.7	0.08
Race (%)						
Asian	1.6	0.8	0.07	1.3	1.2	0.01
Black	13.4	15.0	0.04	13.8	13.8	<.001
white	74.4	72.7	0.04	74.3	74..1	0.005
Unknown	10.1	10.2	0.005	10.2	11.1	0.03
Marital status (%)						
Never Married	19.6	24.3	0.11 *	19.7	16.9	0.07
Divorced	8.3	7.4	0.03	8.4	9.5	0.04
Widowed	2.9	1.8	0.07	2.8	2.7	0.007
Adverse socioeconomic determinants of health (%)	34.2	39.4	0.11 *	34.1	33.2	0.02
Personal history of psychological trauma (%)	8.5	8.9	0.02	8.6	8.4	0.004
Family history of mental and behavioral disorders (%)	15.3	17.7	0.06	15.4	14.3	0.03
Problems related to lifestyle (%)	30.1	32.0	0.04	29.9	29.7	0.005
Pre-existing medical conditions (%)						
Depression	88.7	87.7	0.03	88.3	89.2	0.03
Mood disorders including bipolar disorders	96.0	96.3	0.02	95.8	96.3	0.02
Anxiety	89.7	90.1	0.01	89.6	90.6	0.04
psychotic disorders	21.7	24.8	0.07	21.8	22.2	0.008

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	**Non-GLP1R agonists anti-obesity medications**	**SMD**	**Semaglutide**	**Non-GLP1R agonists anti-obesity medications**	**SMD**
Behavioral disorders including sleep disorders	30.8	25.2	0.13*	30.6	29.7	0.02
Disorders of adult personality and behavior	27.9	27.7	0.005	27.7	27.3	0.01
Sleeping disorders including insomnia	71.3	61.6	0.21*	70.5	72.4	0.04
Suicide attempt	6.2	7.4	0.05	6.4	5.0	0.06
Intentional self-harm	4.8	8.4	0.15*	4.7	3.7	0.05
Personal history of self-harm	20.0	27.6	0.18*	20.5	19.1	0.04
Chronic pain	53.2	46.6	0.13*	52.4	54.5	0.04
Alcohol use disorder	20.5	32.8	0.26*	20.8	21.5	0.02
Tobacco use disorder	38.9	46.7	0.16*	39.0	37.0	0.04
Opioid use disorder	11.3	17.6	0.18*	11.6	12.5	0.03
Cannabis use disorder	16.9	22.6	0.14*	17.2	17.7	0.01
Cocaine use disorder	6.7	12.2	0.19*	6.8	7.3	0.02
Other stimulant disorders	8.0	11.7	0.13*	8.0	7.2	0.03
Other psychoactive substance related disorders	16.0	23.4	0.19*	16.3	17.6	0.03
Type 2 diabetes	56.2	25.6	0.66*	54.8	55.4	0.01
Cancer	42.2	32.7	0.20*	41.3	43.6	0.05
Traumatic brain injury	11.0	10.4	0.02	10.8	10.6	0.004
Prior medication prescription or procedures (%)						
Bariatric surgery	7.7	6.5	0.05	7.9	7.1	0.03
Antidepressants	91.7	91.0	0.03	91.4	92.0	0.02
Antipsychotics	72.2	75.0	0.06	72.8	75.5	0.06
Antiepileptics	77.9	73.0	0.11*	77.6	78.3	0.02
Bezodiazepine derivative sedatives/hypnotics	83.3	79.0	0.11*	83.0	83.9	0.03
Esketamine	1.1	0.7	0.04	1.2	1.2	<.001
Ketamine	13.8	12.1	0.05	13.3	14.3	0.03
Lithium	2.4	3.0	0.04	2.4	2.2	0.02
Bupropion	41.7	45.1	0.07	42.4	45.4	0.07
Naltrexone	8.8	10.5	0.06	9.0	8.2	0.03
Phentermine	10.4	6.1	0.16*	10.4	10.8	0.01
Orlistat	1.9	0.7	0.11*	1.6	1.7	0.009
Topiramate	26.2	27.6	0.03	26.7	25.7	0.02
Insulins	36.4	17.8	0.43*	34.6	34.8	0.005

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	Non-GLP1R agonists anti-obesity medications	SMD	Semaglutide	Non-GLP1R agonists anti-obesity medications	SMD
Metformin	54.4	20.1	0.76*	53.1	50.8	0.05
Alpha glucosidase inhibitors	1.1	0.2	0.11*	0.6	0.0	0.07
Dipeptidyl peptidase 4 (DPP-4) inhibitors	10.5	2.2	0.35*	9.0	9.2	0.008
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	9.9	1.8	0.35*	8.7	8.6	0.004
Sulfonylureas	16.6	4.3	0.41*	15.3	16.2	0.03
Thiazolidinediones	2.7	1.0	0.13*	2.7	2.2	0.03

SMD – standardized mean differences.

*SMD greater than 0.1, indicating cohort imbalance.

Extended Data Table 2|

Characteristics of the semaglutide and non-GLP1R agonists anti-diabetes medications groups for the study population of patients with T2DM who had a prior history of suicidal ideations

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	Non-GLP1R agonists anti-diabetes medications	SMD	Semaglutide	Non-GLP1R agonists anti-diabetes medications	SMD
Total number	253	16,717		251	251	
Age at index event (years, mean±standard deviation)	50.0 ± 13.2	51.23± 15.1	0.09	50.0 ± 13.3	49.9 ± 14.5	0.01
Sex (%)						
Female	60.1	48.1	0.24*	59.8	62.2	0.05
Male	39.9	51.8	0.24*	40.2	37.8	0.05
Ethnicity (%)						
Hispanic/Latinx	9.1	10.1	0.03	9.2	7.6	0.06
Not Hispanic/Latinx	75.1	72.0	0.07	75.3	74.1	0.03
Unknown	15.8	17.9	0.06	15.5	18.3	0.07
Race (%)						
Asian	6.3	2.3	0.20*	6.0	6.8	0.03
Black	11.9	23.8	0.32*	12.0	11.2	0.03
white	64.8	59.4	0.11*	65.3	64.9	0.008
Unknown	14.2	12.8	0.04	13.9	13.9	<.001
Marital status (%)						
Never Married	19.4	20.1	0.02	19.5	17.1	0.06
Divorced	7.5	8.4	0.03	7.6	11.2	0.12*

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	**Non-GLP1R agonists anti-diabetes medications**	**SMD**	**Semaglutide**	**Non-GLP1R agonists anti-diabetes medications**	**SMD**
Widowed	4.0	4.0	0.001	4.0	4.0	<.001
Adverse socioeconomic determinants of health (%)	27.7	27.6	0.002	27.9	25.1	0.06
Personal history of psychological trauma (%)	4.0	4.4	0.02	4.0	4.0	<.001
Family history of mental/ behavioral disorders (%)	8.7	8.1	0.02	8.8	8.0	0.03
Problems related to lifestyle (%)	24.9	19.7	0.13*	24.7	21.1	0.09
Pre-existing medical conditions (%)						
Depression	84.6	75.4	0.23*	84.5	80.5	0.11*
Mood disorders including bipolar disorders	94.1	87.7	0.22*	94.0	92.4	0.06
Anxiety	78.7	70.4	0.19*	78.9	79.3	0.01
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	26.1	32.5	0.14*	25.9	27.1	0.03
Behavioral disorders	23.7	10.7	0.35*	23.5	20.7	0.07
Disorders of adult personality and behavior	25.3	19.8	0.13*	25.1	23.5	0.04
Sleeping disorders including insomnia	668	42.6	0.50*	66.9	66.5	0.008
Suicide attempt	7.9	3.6	0.19*	8.0	5.2	0.11*
Intentional self-harm	8.3	5.2	0.12*	8.4	5.6	0.11*
Personal history of self-harm	17.9	12.9	0.14*	17.9	17.9	0.02
Chronic pain	45.8	36.2	0.20*	46.2	51.4	0.10*
Alcohol use disorder	24.9	29.6	0.11*	25.1	26.7	0.04
Tobacco use disorder	40.7	47.8	0.14*	41.0	40.2	0.02
Opioid use disorder	12.3	14.2	0.06	12.4	15.9	0.10*
Cannabis use disorder	12.3	17.6	0.15*	12.4	14.7	0.07
Cocaine use disorder	11.9	16.9	0.15*	12.0	11.2	0.03
Other stimulant disorders	7.5	8.2	0.03	7.6	7.6	<.001
Other psychoactive substance related disorders	19.0	21.3	0.06	19.1	21.1	0.05
Overweight and obesity	75.1	43.1	0.69*	74.9	79.7	0.11*
Cancer	41.9	27.3	0.31*	41.4	44.2	0.06
Traumatic brain injury	8.7	7.7	0.04	8.8	6.4	0.09
Prior medication prescription or procedures (%)						
Bariatric surgery	4.0	1.8	0.13*	4.0	4.0	<.001

	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	**Non-GLP1R agonists anti-diabetes medications**	**SMD**	**Semaglutide**	**Non-GLP1R agonists anti-diabetes medications**	**SMD**
Antidepressants	87.4	72.6	0.37 *	87.3	87.3	<.001
Antipsy chotics	67.6	62.4	0.11 *	67.7	66.5	0.03
Antiepileptics	76.7	60.7	0.35 *	76.5	76.1	0.009
Bezodiazepine derivative sedatives/hypnotics	83.4	70.6	0.31 *	83.7	84.5	0.02
Esketamine	4.0	0.7	0.22 *	4.0	4.0	<.001
Ketamine	11.1	6.2	0.18 *	11.2	10.4	0.03
Lithium	4.0	1.9	0.12 *	4.0	4.0	<.001
Bupropion	25.7	16.2	0.24 *	25.5	24.3	0.03
Naltrexone	4.0	2.4	0.26 *	4.0	4.0	<.001
Phentermine	4.0	0.6	0.23 *	4.0	4.0	<.001
Orlistat	4.0	0.3	0.26 *	4.0	4.0	<.001
Topiramate	17.4	8.3	0.27 *	17.1	19.1	0.05
Insulins	74.3	45.2	0.62 *	74.1	75.3	0.03
Metformin	72.3	39.6	0.70 *	72.1	72.1	<.001
Alpha glucosidase inhibitors	0.0	0.2	0.06	0.0	0.0	<.001
Dipeptidyl peptidase 4 (DPP-4) inhibitors	23.7	6.6	0.49 *	23.5	23.5	<.001
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	9.1	1.2	0.37 *	8.4	9.2	0.03
Sulfonylureas	31.6	15.9	0.38 *	31.5	33.1	0.03
Thiazolidinediones	7.5	3.3	0.19 *	7.2	6.0	0.05

SMD – standardized mean differences.

* SMD greater than 0.1, indicating cohort imbalance.

Extended Data Table 3|

Clinical diagnosis, medications, procedures, and other codes

Suicidal ideations	**Suicidal ideations (ICD-10 code: R45.851)**
Overweight or obesity	Overweight and obesity (ICD-10 code: E66) Body mass index [BMI] 40 or greater, adult (ICD-10 code: Z68.4) Body mass index [BMI] 30-39, adult (ICD-10 code: Z68.3) Body mass index [BMI] 25.0-25.9, adult (ICD-10 code: Z68.25) Body mass index [BMI] 26.0-26.9, adult (ICD-10 code: Z68.26) Body mass index [BMI] 27.0-27.9, adult (ICD-10 code: Z68.27) Body mass index [BMI] 28.0-28.9, adult (ICD-10 code: Z68.28) Body mass index [BMI] 29.0-29.9, adult (ICD-10 code: Z68.29)
T2DM	Type 2 diabetes mellitus (ICD-10 code: E11)
Other GLP1R agonists medications	lixisenatide (RxNorm code: 1440051), albiglutide (RxNorm code: 1534763), dulaglutide (RxNorm code: 1551291) liraglutide (RxNorm code: 475968), exenatide (RxNorm code: 60548), tirzepatide (RxNorm code: 2601723)
Semaglutide	Semaglutide (RxNorm code: 1991302)

Suicidal ideations	Suicidal ideations (ICD-10 code: R45.851)
non-GLP1R agonists anti-obesity medications	Orlistat (RxNorm code: 37925), Phentermine (RxNorm code 8152), Topiramate (RxNorm code 38404), bupropion (RxNorm code 42347), naltrexone (RxNorm code 7243)
Non-GLP1R agonists anti-diabetes medications	Drugs used in diabetes (ATC code: A10) with GLP1R agonists excluded
Suicidal ideations	Suicidal ideations (ICD-10 code: R45.851)
Medications related to suicidal ideation pharmacotherapy	Antidepressants (ATC code: N06A), Antipsychotics (ATC code: N05A), Antiepileptics (ATC code: N03), Benzodiazepine derivative sedatives/hypnotics (VA code: CN302), Esketamine (RxNorm code: 2119365), Ketamine (RxNorm code: 6130), Lithium (RxNorm code:6448)
Age at the index event	Age
Female	F
Male	M
Asian	Asian (Demographics: 2028-9)
Black or African American	Black or African American (Demographics: 2054-5)
white	white (Demographics: 2106-3)
Hispanic/Latino	Hispanic or Latino (Demographics: 2135-2)
Not Hispanic or Latino	Not Hispanic or Latino (Demographics: 2186-5)
Unknown race	Unknown Race (Demographics: 2131-1)
Unknown ethnicity	Unknown Ethnicity (Demographics: UN)
Divorced	Divorced (Demographics: D)
Widowed	Widowed (Demographics: W)
Never married	Never Married (Demographics: S)
Adverse socioeconomic and psychosocial circumstances	Persons with potential health hazards related to socioeconomic and psychosocial circumstances (ICD-10 code: Z55-Z65), including Problems related to education (Z55), employment/unemployment (Z56), housing and economic circumstances (Z59), social environment (Z60), upbringing (Z62), family circumstances (Z63), psychosocial circumstances (Z64, Z65)
Personal history of psychological trauma	Personal history of psychological trauma, not elsewhere classified (ICD-10 code: Z91.4)
Family history of mental disorders	Family history of mental and behavioral disorders (ICD-10 code: Z81)
Problems related to lifestyle	Problems related to lifestyle (ICD-10 code: Z72)
Depression	Depressive episode (ICD-10 code: F32)
Mood disorders	Mood [affective] disorders (ICD-10 code: F30-F39)
Anxiety	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (ICD-10 code: F40-F48)
Psychotic disorders	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (ICD-10 code: F20-F29)
Behavioral disorders	Behavioral syndromes associated with physiological disturbances and physical factors (ICD-10 code: F50-F59)
Disorders of adult personality and behavior	Disorders of adult personality and behavior (ICD-10 code: F60-F69)
Sleeping disorders including insomnia	Sleeping disorders (ICD-10 code: G47)
Suicide attempt	Suicide attempt (ICD-10 code: T14.91)
Intentional self-harm	Intentional self-harm (ICD-10 code: X71-X83)
Personal history of self-harm	Personal history of self-harm (ICD-10 code: Z91.5)

Suicidal ideations	Suicidal ideations (ICD-10 code: R45.851)
Chronic pain	Chronic pain, not elsewhere classified (ICD-10 code: G89.2)
Alcohol use disorder	Alcohol use disorders (ICD-10 code: F10)
Tobacco use disorder	Nicotine dependence (ICD-10 code: F17)
Opioid use disorder	Opioid use disorders (ICD-10 code: F11
Cannabis use disorder	Cannabis use disorders (ICD-10 code: F12)
Cocaine use disorder	Cocaine use disorders (ICD-10 code: F14)
Other stimulant disorders	Other stimulant disorders (ICD-10 code: F15)
Other psychoactive substance use disorders	Other psychoactive substance related disorders (ICD-10 code: F19)
Cancer	Neoplasms (ICD-10 code: C00-D49)
Traumatic brain injury	Intracranial injury (ICD-10 code: S06)
Bariatric surgery	Bariatric surgery (ICD-10 code: Z98.84)
Insulins	Insulins and analogues (ATC code: A10A
Metformin	Metformin (RxNorm code: 6809)
Sulfonylureas	Sulfonylureas (ATC code: A10BB)
Alpha glucosidase inhibitors	Alpha glucosidase inhibitors (ATC code: A10BF)
Thiazolidinedione	Thiazolidinediones (ATC code: A10BG)
Dipeptidyl peptidase 4 (dpp-4) inhibitors	Dipeptidyl peptidase 4 (dpp-4) inhibitors (ATC code: A10BH)
SGLT2 inhibitors	Sodium-glucose co-transporter 2 (sglt2) inhibitors (ATC code: A10BK)

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Data availability

This study used population-level aggregate and de-identified data collected by the TriNetX Platform, which are available from TriNetX (https://trinetx.com/); however, third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred and a data-sharing agreement would be necessary. Data specific to this study, including diagnosis codes and group characteristics in aggregated format, are included in the paper as tables, figures and supplementary files.

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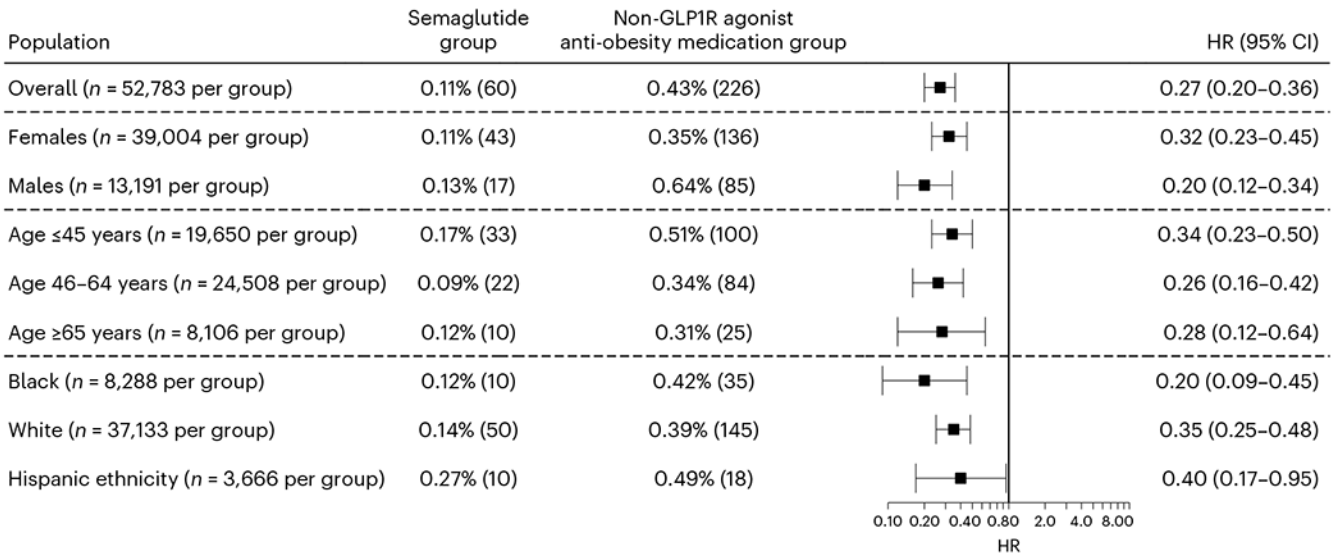

Fig. 1|. Incident suicidal ideations in the study population with overweight or obesity.

Comparison of the incident (first-time experience of) suicidal ideation in the study population with overweight or obesity and no previous history of suicidal ideation (before the index event of the first prescription of semaglutide or non-GLP1R agonist anti-obesity medications that occurred from 1 June 2021 through to 31 December 2022) between the propensity score-matched semaglutide and non-GLP1R agonist anti-obesity medication groups within a 6-month time window after the index event. For each group, the overall risk (number of cases) is shown, where overall risk is defined as the number of patients with outcomes during the 6-month time window divided by the number of patients in the group at the beginning of the time window. HRs were calculated using Kaplan–Meier analysis to estimate the probability of outcome at daily time intervals with censoring applied.

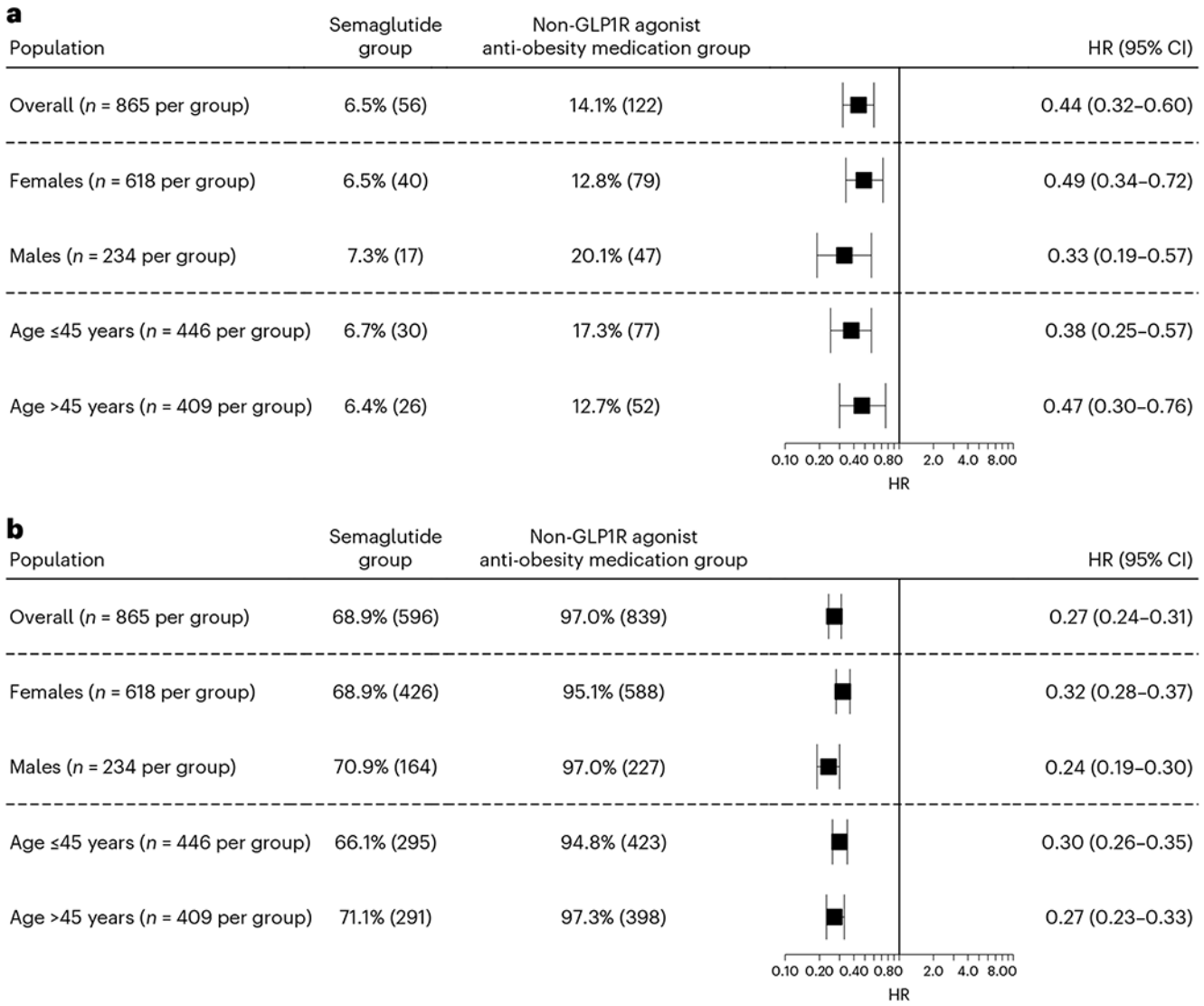

Fig. 2|. Recurrent experience of suicidal ideation and medication prescription for suicidal ideation treatment in the study population with overweight or obesity.

a,**b**, Comparison of recurrent experience of suicidal ideation (**a**) and medication prescription for suicidal ideation treatment (**b**) in the study population with overweight or obesity and a previous history of suicidal ideation (before the index event of the first prescription of semaglutide versus non-GLP1R agonist anti-obesity medications that occurred from 1 June 2021 through to 31 December 2022) between the propensity score-matched semaglutide and non-GLP1R agonist anti-obesity medication groups within a 6-month time window after the index event. For each group, the overall risk (number of cases) is shown, where overall risk is defined as the number of patients with outcomes during the 6-month time window divided by the number of patients in the group at the beginning of the time window. HRs were calculated using Kaplan–Meier analysis to estimate the probability of outcome at daily time intervals with censoring applied.

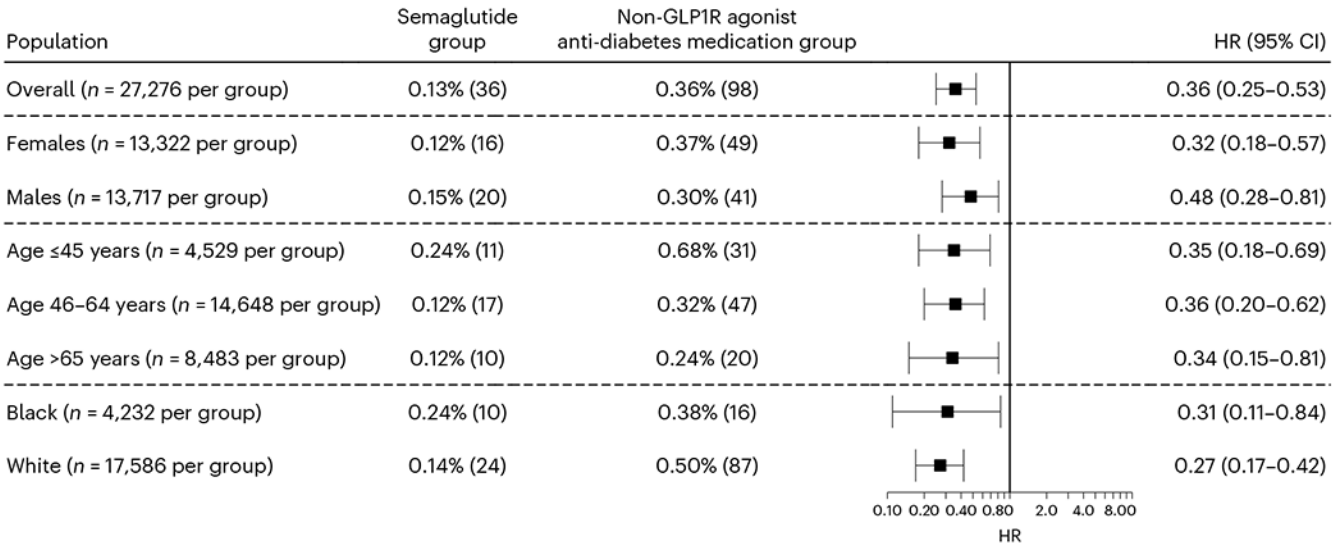

Fig. 3|. Incident suicidal ideations in the study population with T2DM.

Comparison of incident (first-time experience) suicidal ideation In the study population with T2DM and no history of suicidal ideation before the index event of the first prescription of semaglutide or other non-GLP1R agonist anti-diabetes medications that occurred from 1 December 2017 through to 31 May 2021 between the propensity score-matched semaglutide and non-GLP1R agonist anti-diabetes medication groups within the 6-month time window after the index event. For each group, the overall risk (number of cases) is shown, where overall risk is defined as the number of patients with outcomes during the 6-month time window divided by number of patients in the group at the beginning of the time window. HRs were calculated using Kaplan–Meier analysis to estimate the probability of outcome at daily time intervals with censoring applied.

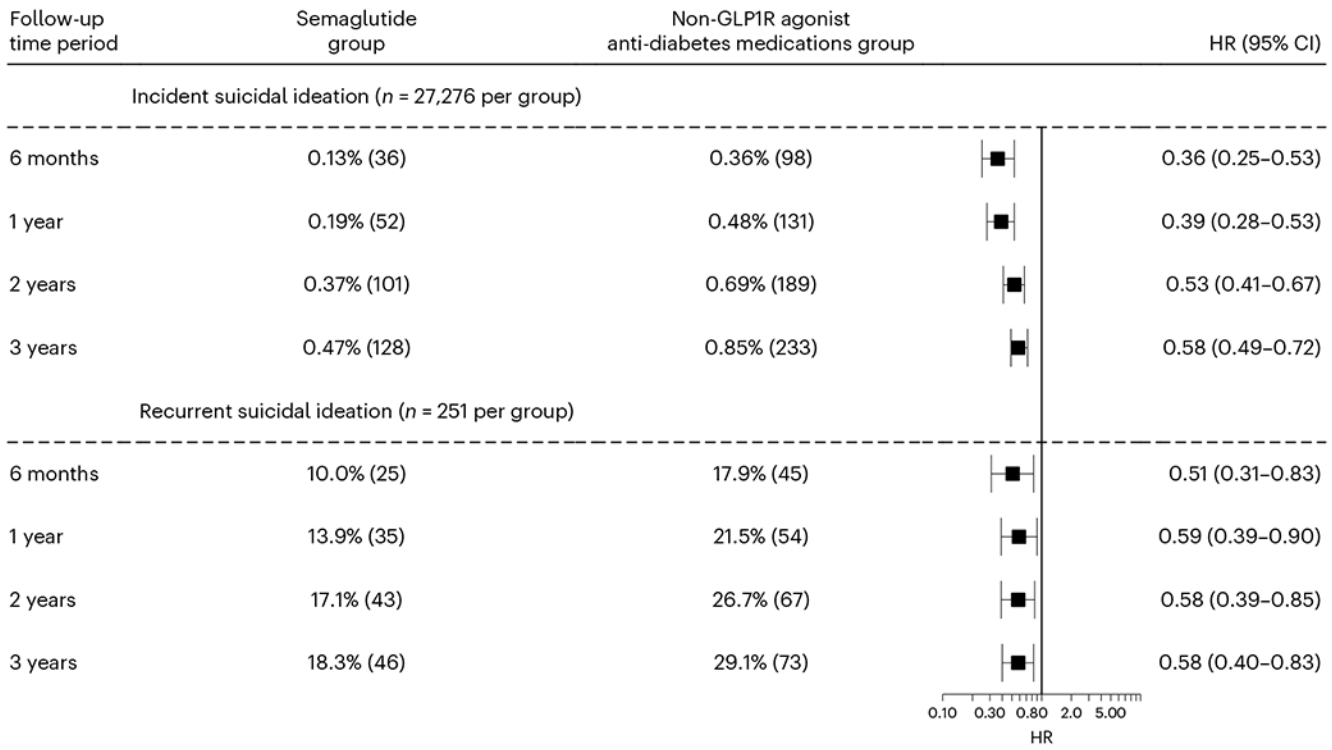

Fig. 4|. Incident and recurrent suicidal ideations in the study population with T2DM at different follow-up time periods.

Comparison of incident and recurrent suicidal ideation in the study population with T2DM between the propensity score-matched semaglutide and non-GLP1R agonist anti-diabetes medication groups at different follow-up time windows (up to 3 years). For each group, the overall risk (number of cases) is shown, where overall risk is defined as the number of patients with outcomes during the 6-month time window divided by the number of patients in the group at the beginning of the time window. HRs were calculated using Kaplan–Meier analysis to estimate the probability of outcome at daily time intervals with censoring applied.

Table 1 |

Characteristics of the semaglutide and non-GLP1R agonist anti-obesity medication groups for the study population with overweight or obesity and no history of suicidal ideation before the index event (first prescription of semaglutide or non-GLP1R agonist anti-obesity medications from 1 June 2021 through to 31 December 2022), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-obesity medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-obesity medication group**	**SMD**
Total number	67,804	164,967		52,783	52,783	
Age at the index event, years, mean±s.d.	51.6±13.5	47.5±15.3	0.29[a]	50.0±13.4	50.3±15.1	0.03
Sex (%)						
Female	67.7	75.2	0.17[a]	72.6	72.5	0.002
Male	31.8	24.3	0.17[a]	26.9	27.0	0.002
Ethnicity (%)						
Hispanic/Latino	7.5	7.9	0.01	7.6	7.3	0.008
Non-Hispanic/Latino	69.9	76.9	0.16[a]	70.9	71.4	0.01
Unknown	22.6	15.3	0.19[a]	21.6	21.3	0.008
Ethnic group (%)						
Asian	2.6	0.9	0.13[a]	1.6	1.7	0.004
Black	16.0	14.9	0.03	15.9	16.1	0.007
White	68.1	71.7	0.08	69.6	69.5	0.002
Unknown	12.0	11.9	0.003	12.0	11.7	0.008
Marital status (%)						
Never married	12.5	17.3	0.14[a]	13.4	13.1	0.009
Divorced	5.5	6.0	0.02	5.6	5.6	<0.001
Widowed	3.6	3.6	0.003	3.4	3.5	0.006
Adverse socioeconomic determinants of health (%)	4.1	6.2	0.10[a]	4.4	4.6	0.01
Personal history of psychological trauma (%)	0.2	0.4	0.05	0.2	0.2	0.005
Family history of mental and behavioral disorders (%)	0.6	1.1	0.06	0.7	0.7	0.005
Lifestyle-related problems (%)	7.9	10.7	0.09	8.2	8.5	0.01

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	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-obesity medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-obesity medication group**	**SMD**
Pre-existing medical conditions (%)						
Depression	26.9	40.7	0.30[a]	30.2	31.9	0.04
Mood disorders, including bipolar disorder	32.0	48.0	0.33[a]	35.9	37.6	0.04
Anxiety, dissociative, somatoform and other nonpsychotic mental disorders, including posttraumatic stress disorder	37.2	48.7	0.23[a]	40.3	41.4	0.02
Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders	1.0	2.0	0.08	1.2	1.2	0.004
Behavioral disorders, including sleep disorders	9.2	10.9	0.06	9.7	10.0	0.009
Disorders of adult personality and behavior, including impulse and gender identity disorders	1.1	2.3	0.09	1.2	1.4	0.01
Symptoms and signs involving an emotional state	4.0	5.4	0.07	4.2	4.5	0.01
Sleeping disorders including insomnia	39.5	37.0	0.05	38.0	38.8	0.02
Chronic pain	25.3	26.9	0.04	25.2	26.0	0.02
Alcohol use disorder	2.4	5.2	0.15[a]	2.7	3.0	0.02
Tobacco use disorder	11.7	17.9	0.18[a]	12.4	13.0	0.02
Opioid use disorder	1.5	3.0	0.10[a]	1.7	1.9	0.01
Cannabis use disorder	1.1	2.4	0.10[a]	1.2	1.4	0.02
Cocaine use disorder	0.4	1.1	0.08	0.5	0.6	0.01
Other stimulant-related disorders	0.4	1.0	0.06	0.5	0.6	0.01
Other psychoactive substance-related disorders	1.0	2.4	0.11[a]	1.1	1.3	0.02
T2DM	44.8	15.6	0.67[a]	30.6	31.7	0.02
Cancer	32.6	29.5	0.07	30.7	31.1	0.008
Traumatic brain injury	2.1	3.1	0.06	2.3	2.4	0.009
Previous medication prescription or procedures (%)						
Bariatric surgery	4.4	5.4	0.05	4.9	5.1	0.007
Antidepressants	44.0	60.4	0.33[a]	48.1	49.7	0.03
Antipsychotics	16.2	22.7	0.17[a]	17.4	18.0	0.02

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	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-obesity medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-obesity medication group**	**SMD**
Antiepileptics	32.1	40.8	0.18[a]	33.4	34.7	0.03
Benzodiazepine-derivative sedatives or hypnotics	44.0	47.0	0.06	43.5	44.2	0.01
Esketamine	0.1	0.2	0.03	0.1	0.1	0.006
Ketamine	5.2	6.4	0.05	5.5	5.6	0.004
Lithium	0.1	0.2	0.03	0.1	0.1	0.005
Bupropion	15.2	30.5	0.37[a]	18.6	20.8	0.05
Naltrexone	3.6	3.7	0.006	4.1	4.1	<0.001
Phentermine	10.4	13.3	0.09	12.2	12.6	0.01
Orlistat	0.6	0.5	0.02	0.6	0.6	0.006
Topiramate	9.5	17.7	0.24[a]	11.6	12.4	0.03
Insulin	21.5	9.8	0.33[a]	15.0	15.8	0.02
Metformin	39.1	13.0	0.62[a]	25.6	27.3	0.04
Alpha glucosidase inhibitors	0.2	0.1	0.03	0.1	0.1	0.005
DPP-4 inhibitors	8.2	1.5	0.32[a]	3.4	3.8	0.02
SGLT2 inhibitors	10.3	1.5	0.38[a]	3.5	4.0	0.03
Sulfonylureas	11.6	2.6	0.36[a]	5.5	6.2	0.03
Thiazolidinediones	2.7	0.7	0.16[a]	1.4	1.6	0.01

The status of variables was based on the presence of related clinical codes any time to 1 day before the index event.

[a]SMD greater than 0.1, a threshold indicating group imbalance.

SMD, standardized mean difference.

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Table 2 |

Characteristics of the semaglutide group and non-GLP1R agonist anti-diabetes medication group for the study population with T2DM and no history of suicidal ideation before the index event (first prescription of semaglutide or other non-GLP1R agonist anti-diabetes medications from 1 December 2017 to 31 May 2021), before and after propensity score matching for the listed variables

	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**
Total number	27,282	1,545,603		27,276	27,726	
Age at the index event, years, mean±s.d.	57.5±12.5	62.0±15.2	0.32[a]	57.5±12.5	57.4±14.4	0.006
Sex (%)						
Female	48.8	47.6	0.02	48.8	49.5	0.006
Male	50.3	52.1	0.04	50.3	49.7	0.01
Ethnicity (%)						
Hispanic/Latino	5.8	9.6	0.14[a]	5.8	5.8	0.001
Non-Hispanic/Latino	66.1	62.6	0.08	66.1	68.0	0.04
Unknown	28.1	27.9	0.005	28.1	26.2	0.04
Ethnic grouping (%)						
Asian	4.6	4.5	0.003	4.6	4.0	0.03
Black	15.5	17.8	0.06	15.5	15.3	0.007
White	64.5	61.6	0.06	64.5	66.0	0.03
Unknown	13.7	15.0	0.04	13.7	13.1	0.02
Marital status (%)						
Never married	9.4	10.1	0.03	9.4	9.5	0.005
Divorced	4.8	4.4	0.02	4.8	5.1	0.02
Widowed	5.0	6.5	0.07	5.0	5.8	0.04
Adverse socioeconomic determinants of health, personal and family history, lifestyle factors (%)	2.4	2.1	0.02	2.4	2.3	0.009
Personal history of psychological trauma	0.1	0.1	0.01	0.1	0.1	0.002
Family history of mental and behavioral disorders	0.3	0.2	0.01	0.3	0.3	0.001
Lifestyle-related problems	5.8	4.4	0.06	5.8	5.4	0.01

	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**
Pre-existing medical conditions (%)						
Depression	17.9	12.8	0.14[a]	17.9	17.9	<0.001
Mood disorders, including bipolar disorders	21.1	15.1	0.16[a]	21.1	21.0	0.001
Anxiety, dissociative, somatoform and other nonpsychotic mental disorders, including posttraumatic stress disorder	21.9	14.4	0.19[a]	21.9	21.6	0.007
Schizophrenia, schizotypal, delusional and other non-mood psychotic disorders	1.1	1.8	0.06	1.1	0.9	0.02
Behavioral disorders, including sleep disorders	4.7	2.5	0.12[a]	4.7	4.6	0.007
Disorders of adult personality and behavior, including impulse and gender identity disorders	0.7	0.7	0.003	0.7	0.7	0.002
Symptoms and signs involving an emotional state	2.4	2.1	0.02	2.4	2.3	0.007
Sleeping disorders including insomnia	29.4	16.8	0.30[a]	29.4	29.1	0.006
Chronic pain	17.1	11.2	0.17[a]	17.1	16.9	0.007
Alcohol use disorder	2.2	3.1	0.06	2.2	2.0	0.009
Tobacco use disorder	12.1	11.4	0.02	12.1	11.4	0.02
Opioid use disorder	1.2	1.2	0.005	1.2	1.0	0.01
Cannabis use disorder	0.8	1.1	0.03	0.8	0.7	0.01
Cocaine use disorder	0.5	0.8	0.03	0.5	0.4	0.02
Other stimulant-related disorders	0.4	0.4	0.004	0.4	0.3	0.003
Other psychoactive substance-related disorders	0.9	1.0	0.02	0.9	0.8	0.01
Overweight and obesity	46.3	23.5	0.49[a]	46.3	47.0	0.01
Cancer	28.4	23.5	0.11[a]	28.4	28.0	0.007
Traumatic brain injury	1.5	1.6	0.01	1.5	1.4	0.008
Previous medication prescription or procedures (%)						
Bariatric surgery	1.6	0.7	0.09	1.6	1.5	0.002
Antidepressants	29.8	20.7	0.21[a]	29.8	29.6	0.005
Antipsychotics	10.8	9.1	0.06	10.8	10.1	0.02
Antiepileptics	26.6	19.5	0.17[a]	25.7	25.6	0.001

	Before propensity score matching			After propensity score matching		
	Semaglutide group	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**	**Semaglutide group**	**Non-GLP1R agonist anti-diabetes medication group**	**SMD**
Benzodiazepine-derivative sedatives or hypnotics	36.2	28.5	0.17[a]	36.2	35.4	0.02
Esketamine	0.2	0.2	0.01	0.2	0.2	0.002
Ketamine	2.8	2.1	0.05	2.8	2.7	0.007
Lithium	0.1	0.1	0.005	0.1	0.1	0.01
Bupropion	6.3	3.1	0.15[a]	6.3	6.4	0.001
Naltrexone	0.7	0.2	0.08	0.7	0.7	0.002
Phentermine	2.0	0.4	0.15[a]	2.0	2.0	0.004
Orlistat	0.3	0.1	0.04	0.3	0.2	0.009
Topiramate	3.2	1.3	0.12[a]	3.0	3.2	0.009
Insulin	43.0	22.1	0.46[a]	43.0	43.6	0.01
Metformin	60.0	27.3	0.70[a]	60.0	61.5	0.03
Alpha glucosidase inhibitors	0.4	0.2	0.04	0.4	0.4	0.005
DPP-4 inhibitors	21.6	6.4	0.45[a]	21.6	21.6	<0.001
SGLT2 inhibitors	17.9	1.5	0.56[a]	17.9	16.6	0.04
Sulfonylureas	28.0	13.1	0.38	27.9	28.3	0.008
Thiazolidinediones	6.6	2.9	0.17[a]	6.6	6.7	0.003

The status of variables was based on the presence of related clinical codes any time to 1 day before the index event.

[a]SMD greater than 0.1, a threshold indicating group imbalance.