Supplementary Material

**Semaglutide and opioid overdose risk in patients with type 2 diabetes and comorbid opioid use disorder: target trial emulation using real-world data**

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# **TriNetX Analytics Platform**

The data used in this study were collected and analyzed on July 20, 2024 within the TriNetX Analytics platform based on the“Research US Collaborative Network”. We used the TriNetX platform to access aggregated and de-identified electronic health records (EHRs) of 116.6 million patients from 66 healthcare organizations in the US across 50 states, covering diverse geographic regions, age, race/ethnic, income and insurance groups and clinical setting. TriNetX, LLC 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 data set 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 analytic functions (e.g., incidence, prevalence, outcomes analysis, survival analysis, propensity score matching) allow for patient-level analyses, while only reporting population level data. The MetroHealth System, Cleveland OH, IRB determined research using TriNetX, in the way described here, is not Human Subject Research, and therefore IRB is not required.

TriNetX is a platform that de-identifies and aggregates EHRs 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 US. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care, and specialty treatment providers, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types including various commercial insurances, governmental insurance (Medicare and Medicaid), self-pay/uninsured, worker compensation insurance, military/VA insurance among others.

Self-reported sex (female, male), race 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 Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race; and (2) Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity.

TriNetX completes 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. All covariates are either binary, categorical (which expands to a set of binary columns), or continuous but essentially guaranteed to exist. Missing sex values are represented using “Unknown Sex”. The missing data for race and ethnicity are presented as “Unknown race” or “Unknown Ethnicity”. For other variables including medical conditions, procedures, lab tests and socio-economic determinant health, the value is either present or absent so “missing” is not pertinent.

# **Supplement Table 1**. Specification and emulation of pragmatic target trials.

Comparing the new use of semaglutide with the new use of other anti-diabetes medications for risk of OUD-related outcomes in patients with comorbid T2DM and OUD using EHR data and analytics functions from the TriNetX Analytics Platform. Target trial specifications and emulations were similar unless otherwise stated.

|  |  |  |
| --- | --- | --- |
| **Protocol** | **Specification of Target Trials** | **Emulation of Target Trials** |
| Eligibility criteria | * Prescribed semaglutide or other antidiabetes medications between December 1, 2017 and June 30, 2023 * Had a diagnosis of T2DM and a diagnosis of OUD * had at least one of the diseases based on the prescription guideline for semaglutide (obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, or stroke). * No history of bariatric surgery * No contraindication, warning, and limited use related to semaglutide (pancreatitis, type 1 diabetes, thyroid cancer, and gastroparesis) | Same as for the target trials |
| Treatment strategies | For the target trial comparing semaglutide vs insulins   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of insulins at index event and not initiate semaglutide   For the target trial comparing semaglutide vs metformin   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications * Initiate use of metformin at index event and not initiate semaglutide.   For the target trial comparing semaglutide vs DPP-4i   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of DPP-4i at index event and not initiate semaglutide.   For the target trial comparing semaglutide vs SGLT2i   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of SGLT-2i at index event and not initiate semaglutide.   For the target trial comparing semaglutide vs SU   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of SU at index event and not initiate semaglutide.   For the target trial comparing semaglutide vs TZD   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of TZD at index event and not initiate semaglutide.   For the target trial comparing semaglutide vs other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide)   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of GLP-1RAs at index event and not semaglutide.   For the target trial comparing semaglutide vs liraglutide   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of liraglutide at index event and not semaglutide.   For the target trial comparing semaglutide vs dulaglutide   * Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. * Initiate use of dulaglutide at index event and not semaglutide. | Same as for the target trials. The date of medication initiation was defined as the date of a first medication prescription. |
| **Treatment assignment** | Individuals are randomly assigned to a treatment strategy at baseline. Individuals will be aware of the assigned treatment strategies. | Individuals are assigned to the strategy compatible with their first prescription and assumed randomization by propensity-score matching for baseline covariates. |
| **Outcomes** | * Opioid overdose1 * Negative control outcome: medical encounters for congenital malformations, deformations and chromosomal abnormalities | Same as for the target trials |
| **Follow-up** | Follow-up for each individual will start at treatment assignment and end on day of outcome, death, loss to follow-up, or 12 month after baseline, whichever occurs first. | Same as for the target trials |
| **Casual contrast of interest** | Intention-to-treat: the treatment strategy is assigned at baseline, regardless of medication use adherence, medication switch or add-on. | Observational analog to intention-to-treat |
| **Statistical analysis** | * Kaplan-Meier estimator to obtain cumulative incidences for each treatment strategy within 12 months of follow-up. Compare cumulative incidence between treatment strategies by risk differences. * Cox proportional hazards analyses to compare rates of time-to-events on daily basis during follow-up time since the baseline. * Models are adjusted for confounders at baseline | Same as for the target trial except observational analogs of intention-to-treat analyses required matching for confounding variables by propensity-score matching. |

DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

# **Supplement Table 2**. Eligibility criteria and exposure definitions.

|  |  |  |
| --- | --- | --- |
| **Eligibility criteria** | | |
| **Variable** | **Values** | **Name and Codes** |
| Diagnosis of T2DM | Binary: present/absent | Type 2 diabetes mellitus (ICD-10 code: E11) |
| Diagnosis of OUD | Binary: present/absent | Opioid related disorders (ICD-10 code: F11) |
| Had at least one of the diseases based on the prescription guideline for semaglutide (obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, stroke). | Binary: present/absent | Hypertension (ICD-10: I10-I1A)  Hypercholesterolemia (ICD-10 E78.0)  Hyperlipidemia (ICD-10: E78.2, E78.4, E78.5)  Heart diseases (ICD-10: I20-I25, I30-I5A)  Stroke (ICD-10: I63, I60-I69)  Obesity (E66.0, E66.2, E66.8, E66.9, Z68.30, Z68.31, Z68.32, Z68.33, Z68.34, Z68.35, Z68.36, Z68.37, Z68.38, Z68.39, Z68.30, Z68.30, Z68.39, Z68.41, Z68.42, Z68.43, Z68.44, Z68.45) |
| No history of bariatric surgery | Binary: present/absent | Gastrointestinal System / Bypass / Stomach (ICD-10 Procedure Coding System (PCS): 0D16)  Bariatric surgery status (ICD-10: Z98.84) |
| No contraindication, warning, and limited use where one drug would be preferred over the other (pancreatitis, type 1 diabetes, thyroid cancer, and gastroparesis) | Binary: present/absent | Pancreatitis (ICD-10: K85, K86.0, K86.1)  Type 1 diabetes (ICD-10: E10)  Gastroparesis (ICD-10: K31.84)  Thyroid cancer (ICD-10: C73, Z85.850, E31.2) |
| **Exposure definitions** | | |
| Initiation of semaglutide at baseline | Binary: present/absent | Semaglutide (RxNorm code: 1991302) |
| Initiation of insulins at baseline | Binary: present/absent | Insulins (ATC code: A10A) |
| Initiation of metformin at baseline | Binary: present/absent | Metformin (ATC code: A10BA) |
| Initiation of DPP-4i at baseline | Binary: present/absent | Dipeptidyl peptidase 4 (DPP-4) inhibitors (ATC code: A10BH) |
| Initiation of SGLT2i at baseline | Binary: present/absent | Sodium-glucose co-transporter 2 (SGLT2) inhibitors (ATC code: A10BK) |
| Initiation of SU at baseline | Binary: present/absent | Sulfonylureas (ATC code: A10BB) |
| Initiation of TZD at baseline | Binary: present/absent | Thiazolidinediones (ATC code: A10BF) |
| Initiation of other GLP-1RA at baseline | Binary: present/absent | Albiglutide: RxNorm code: 1534763  Exenatide: RxNorm code: 60548  Dulaglutide: RxNorm code:1551291  Liraglutide: RxNorm code: 475968  Lixisenatide: RxNorm code: 1440051 |
| Initiation of liraglutide at baseline | Binary: present/absent | Liraglutide: RxNorm code: 475968 |
| Initiation of dulaglutide at baseline | Binary: present/absent | Dulaglutide: RxNorm code:1551291 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. ICD-10 – International Classification of Diseases System, version 10; RxNorm – medical prescription normalized Medical prescription; ATC – Anatomical Therapeutic Chemical (ATC) classification system; CPT – Current Procedural Terminology

# **Supplement Figure 1**. Graphical illustration of the study design

A diagram of a patient's medication

Description automatically generated

See Supplement Table 2 for definitions of eligibility criteria, exposure, covariates, and outcomes.

Follow-up for each individual started at treatment assignment and ended on the day of outcome, death, loss to follow-up, or 12 months after baseline, whichever occurred first. T2DM – Type 2 diabetes; OUD – Opioid use disorder.

# **Supplement Table 3**. Outcome definitions.

|  |  |  |
| --- | --- | --- |
| **Eligibility criteria** | | |
| **Variable** | **Values** | **Name and Codes** |
| **Primary outcomes** | | |
| Opioid overdose1 | Binary: present/absent | Poisoning by opium (ICD-10: T40.0X) Poisoning by heroin (ICD-10: T40.1X) Poisoning by other opioids (ICD-10: T40.2X) Poisoning by methadone (ICD-10: T40.3X)  Poisoning by, adverse effect of and underdosing of other synthetic narcotics  (ICD-10: T40.4X) Poisoning by fentanyl or fentanyl analogues (ICD-10: T40.41) Poisoning by tramadol (ICD-10: T40.42) Poisoning by other synthetic narcotics (ICD-10: T40.49) Poisoning by unspecified narcotics (ICD-10: T40.60) Poisoning by other narcotics (ICD-10: T40.69) |
| Negative control outcome | | |
| Congenital malformations, deformations and chromosomal abnormalities | Binary: present/absent | Congenital malformations, deformations and chromosomal abnormalities (ICD-10: Q00-Q99) |

ICD-10 – International Classification of Diseases System, version 10

RxNorm – medical prescription normalized Medical prescription

ATC – Anatomical Therapeutic Chemical (ATC) classification system

CPT – Current Procedural Terminology

HL7V3.0 – Health Level Seven (HL7) Vocabulary, Version 3.0

# **Supplement Table 4**: Definitions of covariates.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Value** | **Code** | **Coding terminology** |
| Age at Index | continuous | AI | Demographics |
| Female | Binary: present/absent | F | Demographics |
| Male | Binary: present/absent | M | Demographics |
| Black or African American | Binary: present/absent | 2054-5 | Demographics |
| White | Binary: present/absent | 2106-3 | Demographics |
| Unknown Race | Binary: present/absent | UNK | Demographics |
| Unknown Gender | Binary: present/absent | UN | Demographics |
| Not Hispanic or Latino | Binary: present/absent | 2186-5 | Demographics |
| Hispanic or Latino | Binary: present/absent | 2135-2 | Demographics |
| Asian | Binary: present/absent | 2028-9 | Demographics |
| Persons with potential health hazards related to socioeconomic and psychosocial circumstances | Binary: present/absent | Z55-Z65 | ICD-10 |
| Problems related to lifestyle | Binary: present/absent | Z72 | ICD-10 |
| Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders | Binary: present/absent | F20-F29 | ICD-10 |
| Mood [affective] disorders | Binary: present/absent | F30-F39 | ICD-10 |
| Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders | Binary: present/absent | F40-F48 | ICD-10 |
| Behavioral syndromes associated with physiological disturbances and physical factors | Binary: present/absent | F50-F59 | ICD-10 |
| Disorders of adult personality and behavior | Binary: present/absent | F60-F69 | ICD-10 |
| Alcohol related disorders | Binary: present/absent | F10 | ICD-10 |
| Nicotine dependence | Binary: present/absent | F17 | ICD-10 |
| Cannabis related disorders | Binary: present/absent | F12 | ICD-10 |
| Cocaine related disorders | Binary: present/absent | F14 | ICD-10 |
| Other stimulant related disorders | Binary: present/absent | F15 | ICD-10 |
| Other psychoactive substance related disorders | Binary: present/absent | F19 | ICD-10 |
| Depressive episode | Binary: present/absent | F32 | ICD-10 |
| Chronic pain, not elsewhere classified | Binary: present/absent | G89.2 | ICD-10 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | Binary: present/absent | F90-F98 | ICD-10 |
| Obesity | Binary: present/absent | E66, Z68.3, Z68.4 | ICD-10 |
| Severe obesity | Binary: present/absent | E66.01 | ICD-10 |
| Drug overdose | Binary: present/absent | T40 | ICD-10 |
| Opioid overdose | Binary: present/absent | T40.0X, T40.1X, T40.2X, T40.3X, T40.4X, T40.41, T40.42, T40.49, T40.60, T40.69 | ICD-10 |
| Methadone | Binary: present/absent | 6813 | RxNorm |
| Buprenorphine | Binary: present/absent | 1819 | RxNorm |
| Naltrexone | Binary: present/absent | 7243 | RxNorm |
| Naloxone | Binary: present/absent | 7242 | RxNorm |
| Opioid analgesics | Binary: present/absent | CN101 | ATC |
| Sedatives/hypontics | Binary: present/absent | CN300 | ATC |
| Insulins and analogues | Binary: present/absent | A10A | ATC |
| Biguanides | Binary: present/absent | A10BA | ATC |
| Sulfonylureas | Binary: present/absent | A10BB | ATC |
| Thiazolidinediones | Binary: present/absent | A10BG | ATC |
| Dipeptidyl peptidase 4 (DPP-4) inhibitors | Binary: present/absent | A10BH | ATC |
| Sodium-glucose co-transporter 2 (SGLT2) inhibitors | Binary: present/absent | A10BK | ATC |
| Other blood glucose lowering drugs, excl. Insulins | Binary: present/absent | A10BX | ATC |
| Glucagon-like peptide-1 (GLP-1) analogues | Binary: present/absent | A10BJ | ATC |
| Liraglutide | Binary: present/absent | 475968 | RxNorm |
| Dulaglutide | Binary: present/absent | 1551291 | RxNorm |
| Exenatide | Binary: present/absent | 60548 | RxNorm |
| Albiglutide | Binary: present/absent | 1534763 | RxNorm |
| Lixisenatide | Binary: present/absent | 1440051 | RxNorm |
| Substance abuse treatment | Binary: present/absent | H | ICD-10 |
| Hospitalizations | Binary: present/absent | 1013659 | CPT |
| Emergency department visit | Binary: present/absent | 1013711 | CPT |

ICD-10 – International Classification of Diseases System, version 10

RxNorm – medical prescription normalized Medical prescription

ATC – Anatomical Therapeutic Chemical (ATC) classification system

CPT – Current Procedural Terminology

# **Supplement Table** 5: Characteristics of the propensity-score matched semaglutide vs metformin groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **metformin** | **SMD** | **semaglutide** | **metformin** | **SMD** |
| **Total number** | 3,034 | 17,785 |  | 2,605 | 2,605 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 57.4± 11.7 | 0.001 | 57.6 ± 11.0 | 57.5 ± 11.8 | 0.01 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 43.1 | 0.27\* | 55.4 | 56.0 | 0.01 |
| Male | 38.6 | 54.1 | 0.32\* | 40.3 | 39.0 | 0.03 |
| Unknown | 4.9 | 2.8 | 0.11\* | 4.4 | 5.0 | 0.03 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 8.7 | 0.07 | 6.8 | 6.2 | 0.03 |
| Not Hispanic/Latinx | 75.6 | 70.6 | 0.11\* | 75.4 | 75.3 | 0.003 |
| Unknown | 17.7 | 20.7 | 0.08 | 17.7 | 18.5 | 0.02 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 0.8 | 0.01 | 0.8 | 0.5 | 0.03 |
| Black | 19.5 | 23.6 | 0.10\* | 19.2 | 19.9 | 0.02 |
| White | 63.0 | 60.3 | 0.06 | 63.3 | 62.7 | 0.01 |
| Unknown | 12.2 | 10.9 | 0.06 | 11.8 | 12.3 | 0.02 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 14.8 | 0.02 | 13.8 | 14.0 | 0.006 |
| **Problems related to lifestyle (%)** | 23.9 | 23.2 | 0.02 | 23.1 | 22.6 | 0.01 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 44.1 | 0.46\* | 63.8 | 65.3 | 0.03 |
| Severe obesity | 53.6 | 26.1 | 0.58\* | 50.5 | 50.6 | 0.002 |
| Depression | 62.8 | 54.4 | 0.17\* | 61.9 | 63.0 | 0.02 |
| Mood disorders | 70.4 | 63.5 | 0.15\* | 69.2 | 71.0 | 0.04 |
| Anxiety disorders | 69.1 | 60.0 | 0.19\* | 68.0 | 68.8 | 0.02 |
| Psychotic disorders | 6.9 | 12.2 | 0.18\* | 7.3 | 7.2 | 0.004 |
| Behavioral disorders | 21.3 | 12.0 | 0.25\* | 19.8 | 19.4 | 0.01 |
| Disorders of adult personality and behavior | 7.4 | 8.1 | 0.03 | 7.2 | 6.9 | 0.01 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 6.2 | 0.11\* | 8.6 | 8.3 | 0.01 |
| Chronic pain | 77.7 | 61.9 | 0.35\* | 76.3 | 75.1 | 0.03 |
| Alcohol use disorder | 13.9 | 23.7 | 0.25\* | 14.4 | 13.6 | 0.02 |
| Nicotine dependence | 44.4 | 55.8 | 0.23\* | 45.2 | 44.8 | 0.008 |
| Cannabis use disorder | 11.9 | 15.2 | 0.09 | 11.6 | 11.9 | 0.007 |
| Cocaine use disorder | 11.8 | 19.3 | 0.21\* | 11.8 | 12.1 | 0.007 |
| Other stimulant disorders | 8.1 | 9.6 | 0.05 | 7.8 | 7.9 | 0.007 |
| Other psychoactive substance related disorders | 22.6 | 31.3 | 0.20\* | 22.8 | 23.1 | 0.007 |
| Drug overdose | 8.8 | 12.1 | 0.11\* | 9.0 | 8.8 | 0.008 |
| Opioid overdose | 3.3 | 4.5 | 0.06 | 3.5 | 3.3 | 0.01 |
| Substance abuse treatment | 2.5 | 4.7 | 0.12\* | 2.8 | 2.6 | 0.01 |
| Methadone | 10.2 | 15.1 | 0.15\* | 10.7 | 10.1 | 0.02 |
| Buprenorphine | 13.9 | 14.1 | 0.007 | 13.6 | 14.5 | 0.03 |
| Naltrexone | 3.6 | 1.9 | 0.10\* | 3.1 | 3.3 | 0.009 |
| Naloxone | 51.3 | 36.9 | 0.29\* | 49.4 | 49.2 | 0.004 |
| Opioid analgesics | 95.1 | 88.9 | 0.23\* | 94.8 | 95.2 | 0.02 |
| Sedatives/Hypontics | 82.9 | 75.0 | 0.20\* | 82.2 | 82.0 | 0.006 |
| Insulin | 63.2 | 57.6 | 0.11\* | 62.2 | 62.4 | 0.004 |
| Metformin | 76.2 | 46.4 | 0.64\* | 73.7 | 74.5 | 0.02 |
| DPP-4i | 18.9 | 8.9 | 0.29\* | 17.7 | 18.1 | 0.01 |
| SGLT2i | 23.8 | 4.1 | 0.59\* | 18.2 | 17.0 | 0.03 |
| SU | 33.1 | 20.7 | 0.28\* | 31.9 | 30.6 | 0.03 |
| TZD | 7.8 | 3.8 | 0.17\* | 7.3 | 7.6 | 0.01 |
| Other GLP-1RAs | 32.1 | 6.2 | 0.70\* | 25.1 | 24.0 | 0.03 |
| Liraglutide | 16.6 | 3.2 | 0.46\* | 13.3 | 12.5 | 0.02 |
| Dulaglutide | 16.7 | 2.5 | 0.50\* | 12.4 | 11.1 | 0.04 |
| Exenatide | 5.5 | 1.7 | 0.21\* | 5.5 | 5.3 | 0.007 |
| Albiglutide | 0.6 | 0.1 | 0.08 | 0.6 | 0.6 | <.001 |
| Lixisenatide | 0.5 | 0.1 | 0.08 | 0.4 | 0.4 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 1.1 | 0.16\* | 2.8 | 2.8 | 0.002 |
| Hospitalizations | 62.5 | 67.2 | 0.09 | 62.5 | 61.3 | 0.02 |
| Emergency department visit | 70.4 | 68.1 | 0.05 | 69.6 | 68.5 | 0.02 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

**Supplement Table 6**: Characteristics of the propensity-score matched semaglutide vs DPP-4i groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **DPP-4i** | **SMD** | **semaglutide** | **DPP-4i** | **SMD** |
| **Total number** | 3,034 | 3,837 |  | 1,751 | 1,751 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 60.5 ± 11.8 | 0.27\* | 58.6 ± 10.9 | 58.5 ± 12.0 | 0.002 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 48.0 | 0.17\* | 53.7 | 52.8 | 0.02 |
| Male | 38.6 | 49.5 | 0.22\* | 42.8 | 43.6 | 0.02 |
| Unknown | 4.9 | 2.5 | 0.13\* | 3.5 | 3.7 | 0.009 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 9.7 | 0.11\* | 7.5 | 7.5 | 0.002 |
| Not Hispanic/Latinx | 75.6 | 70.1 | 0.12\* | 74.4 | 74.5 | 0.001 |
| Unknown | 17.7 | 20.2 | 0.06 | 18.1 | 18.0 | 0.003 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 1.4 | 0.07 | 1.0 | 1.0 | 0.006 |
| Black | 19.5 | 22.4 | 0.07 | 19.9 | 20.6 | 0.02 |
| White | 63.0 | 60.5 | 0.05 | 63.1 | 62.3 | 0.02 |
| Unknown | 12.2 | 10.7 | 0.05 | 11.3 | 11.1 | 0.007 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 13.0 | 0.03 | 12.7 | 13.1 | 0.01 |
| **Problems related to lifestyle (%)** | 23.9 | 23.0 | 0.02 | 22.2 | 22.9 | 0.02 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 45.0 | 0.44\* | 57.3 | 57.9 | 0.01 |
| Severe obesity | 53.6 | 25.7 | 0.59\* | 39.9 | 41.4 | 0.03 |
| Depression | 62.8 | 54.4 | 0.17\* | 58.5 | 58.5 | <.001 |
| Mood disorders | 70.4 | 63.0 | 0.16\* | 65.6 | 66.3 | 0.01 |
| Anxiety disorders | 69.1 | 59.6 | 0.20\* | 64.1 | 64.0 | 0.004 |
| Psychotic disorders | 6.9 | 10.8 | 0.14\* | 8.1 | 8.6 | 0.02 |
| Behavioral disorders | 21.3 | 13.1 | 0.22\* | 16.6 | 16.5 | 0.002 |
| Disorders of adult personality and behavior | 7.4 | 7.6 | 0.005 | 7.1 | 7.6 | 0.02 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 4.8 | 0.17\* | 7.4 | 7.0 | 0.02 |
| Chronic pain | 77.7 | 65.3 | 0.28\* | 72.1 | 73.8 | 0.04 |
| Alcohol use disorder | 13.9 | 18.2 | 0.12\* | 14.7 | 14.7 | <.001 |
| Nicotine dependence | 44.4 | 50.3 | 0.12\* | 46.5 | 46.2 | 0.006 |
| Cannabis use disorder | 11.9 | 12.1 | 0.005 | 11.7 | 11.9 | 0.009 |
| Cocaine use disorder | 11.8 | 15.4 | 0.11\* | 12.5 | 12.2 | 0.009 |
| Other stimulant disorders | 8.1 | 8.3 | 0.006 | 7.5 | 7.4 | 0.002 |
| Other psychoactive substance related disorders | 22.6 | 25.9 | 0.08 | 22.7 | 23.5 | 0.02 |
| Drug overdose | 8.8 | 11.8 | 0.10\* | 9.7 | 8.9 | 0.03 |
| Opioid overdose | 3.3 | 4.7 | 0.07 | 3.8 | 3.7 | 0.003 |
| Substance abuse treatment | 2.5 | 2.5 | 0.001 | 2.6 | 2.7 | 0.007 |
| Methadone | 10.2 | 13.3 | 0.09 | 11.4 | 12.6 | 0.04 |
| Buprenorphine | 13.9 | 11.1 | 0.09 | 12.0 | 12.9 | 0.03 |
| Naltrexone | 3.6 | 1.9 | 0.10\* | 2.7 | 2.7 | <.001 |
| Naloxone | 51.3 | 36.2 | 0.31\* | 44.2 | 46.1 | 0.04 |
| Opioid analgesics | 95.1 | 91.4 | 0.15\* | 94.2 | 94.2 | 0.002 |
| Sedatives/Hypontics | 82.9 | 77.6 | 0.13\* | 80.6 | 80.5 | 0.004 |
| Insulin | 63.2 | 69.1 | 0.13\* | 65.7 | 65.0 | 0.01 |
| Metformin | 76.2 | 68.3 | 0.18\* | 74.0 | 74.0 | 0.001 |
| DPP-4i | 18.9 | 26.3 | 0.18\* | 22.4 | 22.1 | 0.007 |
| SGLT2i | 23.8 | 9.2 | 0.40\* | 17.1 | 17.0 | 0.002 |
| SU | 33.1 | 37.7 | 0.09 | 35.1 | 35.1 | <.001 |
| TZD | 7.8 | 7.6 | 0.009 | 7.6 | 7.8 | 0.006 |
| Other GLP-1RAs | 32.1 | 8.7 | 0.61\* | 18.1 | 16.8 | 0.04 |
| Liraglutide | 16.6 | 4.0 | 0.42\* | 8.6 | 7.7 | 0.03 |
| Dulaglutide | 16.7 | 3.9 | 0.43\* | 9.3 | 8.2 | 0.04 |
| Exenatide | 5.5 | 2.1 | 0.18\* | 3.8 | 3.7 | 0.006 |
| Albiglutide | 0.6 | 0.3 | 0.06 | 0.6 | 0.6 | <.001 |
| Lixisenatide | 0.5 | 0.3 | 0.04 | 0.6 | 0.6 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 2.3 | 0.08 | 2.5 | 2.9 | 0.02 |
| Hospitalizations | 62.5 | 68.0 | 0.12\* | 63.3 | 62.4 | 0.02 |
| Emergency department visit | 70.4 | 67.0 | 0.07 | 67.7 | 67.7 | <.001 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

# **Supplement Table 7**: Characteristics of the propensity-score matched semaglutide vs SGLT2i groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **SGLT2i** | **SMD** | **semaglutide** | **SGLT2i** | **SMD** |
| **Total number** | 3,034 | 5,552 |  | 2,361 | 2,361 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 60.3 ± 11.1 | 0.26\* | 58.2± 10.8 | 58.54± 11.5 | 0.02 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 41.1 | 0.31\* | 53.2 | 53.1 | 0.001 |
| Male | 38.6 | 55.5 | 0.34\* | 42.2 | 42.1 | 0.002 |
| Unknown | 4.9 | 3.4 | 0.08 | 4.7 | 4.8 | 0.006 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 8.7 | 0.07 | 7.2 | 6.6 | 0.02 |
| Not Hispanic/Latinx | 75.6 | 71.8 | 0.09 | 74.4 | 74.6 | 0.005 |
| Unknown | 17.7 | 19.5 | 0.05 | 18.4 | 18.7 | 0.008 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 1.0 | 0.03 | 0.8 | 0.8 | 0.009 |
| Black | 19.5 | 23.1 | 0.09 | 19.9 | 19.8 | 0.001 |
| White | 63.0 | 58.9 | 0.08 | 61.9 | 61.9 | <.001 |
| Unknown | 12.2 | 11.4 | 0.03 | 12.4 | 12.3 | 0.003 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 15.7 | 0.05 | 13.9 | 13.3 | 0.02 |
| **Problems related to lifestyle (%)** | 23.9 | 27.1 | 0.07 | 24.2 | 23.2 | 0.03 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 53.4 | 0.27\* | 62.5 | 64.5 | 0.04 |
| Severe obesity | 53.6 | 33.8 | 0.41\* | 48.3 | 49.5 | 0.02 |
| Depression | 62.8 | 56.6 | 0.13\* | 60.9 | 61.5 | 0.01 |
| Mood disorders | 70.4 | 64.2 | 0.13\* | 68.1 | 68.9 | 0.02 |
| Anxiety disorders | 69.1 | 62.6 | 0.14\* | 67.2 | 67.1 | 0.002 |
| Psychotic disorders | 6.9 | 9.5 | 0.09 | 7.6 | 6.7 | 0.04 |
| Behavioral disorders | 21.3 | 16.5 | 0.12\* | 19.8 | 20.3 | 0.01 |
| Disorders of adult personality and behavior | 7.4 | 6.4 | 0.04 | 7.0 | 6.3 | 0.03 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 5.9 | 0.13\* | 8.1 | 7.5 | 0.02 |
| Chronic pain | 77.7 | 71.4 | 0.15\* | 75.8 | 75.9 | 0.004 |
| Alcohol use disorder | 13.9 | 20.7 | 0.18\* | 15.4 | 15.6 | 0.007 |
| Nicotine dependence | 44.4 | 52.3 | 0.16\* | 46.7 | 45.4 | 0.03 |
| Cannabis use disorder | 11.9 | 12.1 | 0.005 | 12.0 | 11.5 | 0.01 |
| Cocaine use disorder | 11.8 | 16.2 | 0.13\* | 12.1 | 12.1 | 0.001 |
| Other stimulant disorders | 8.1 | 9.7 | 0.06 | 8.0 | 7.7 | 0.01 |
| Other psychoactive substance related disorders | 22.6 | 26.5 | 0.09 | 23.5 | 21.9 | 0.04 |
| Drug overdose | 8.8 | 12.6 | 0.13\* | 9.7 | 9.7 | <.001 |
| Opioid overdose | 3.3 | 4.4 | 0.05 | 3.8 | 3.6 | 0.009 |
| Substance abuse treatment | 2.5 | 2.8 | 0.02 | 2.8 | 2.5 | 0.02 |
| Methadone | 10.2 | 13.4 | 0.10\* | 11.1 | 11.3 | 0.008 |
| Buprenorphine | 13.9 | 15.3 | 0.04 | 13.8 | 14.4 | 0.02 |
| Naltrexone | 3.6 | 2.3 | 0.08 | 3.0 | 3.0 | 0.002 |
| Naloxone | 51.3 | 47.7 | 0.07 | 50.5 | 50.9 | 0.008 |
| Opioid analgesics | 95.1 | 94.1 | 0.05 | 94.5 | 95.0 | 0.02 |
| Sedatives/Hypontics | 82.9 | 81.3 | 0.04 | 82.2 | 82.1 | 0.001 |
| Insulin | 63.2 | 72.0 | 0.19\* | 65.7 | 65.9 | 0.003 |
| Metformin | 76.2 | 70.3 | 0.13\* | 74.8 | 74.7 | 0.004 |
| DPP-4i | 18.9 | 19.7 | 0.02 | 18.8 | 20.8 | 0.05 |
| SGLT2i | 23.8 | 6.3 | 0.50\* | 15.0 | 13.7 | 0.04 |
| SU | 33.1 | 34.7 | 0.03 | 33.2 | 34.3 | 0.02 |
| TZD | 7.8 | 7.0 | 0.03 | 7.6 | 7.8 | 0.008 |
| Other GLP-1RAs | 32.1 | 19.8 | 0.29\* | 27.4 | 27.3 | 0.004 |
| Liraglutide | 16.6 | 8.1 | 0.26\* | 13.8 | 13.3 | 0.01 |
| Dulaglutide | 16.7 | 12.2 | 0.13\* | 15.6 | 15.4 | 0.006 |
| Exenatide | 5.5 | 4.0 | 0.07 | 5.6 | 5.3 | 0.02 |
| Albiglutide | 0.6 | 0.2 | 0.06 | 0.5 | 0.5 | 0.006 |
| Lixisenatide | 0.5 | 0.2 | 0.05 | 0.4 | 0.4 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 2.2 | 0.08 | 2.9 | 3.5 | 0.03 |
| Hospitalizations | 62.5 | 70.1 | 0.16\* | 64.0 | 63.6 | 0.007 |
| Emergency department visit | 70.4 | 71.0 | 0.01 | 69.9 | 69.1 | 0.02 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

# **Supplement Table 8**: Characteristics of the propensity-score matched semaglutide vs SU groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **SU** | **SMD** | **semaglutide** | **SU** | **SMD** |
| **Total number** | 3,034 | 6,091 |  | 2,128 | 2,128 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 59.8 ± 11.8 | 0.21\* | 58.2± 10.9 | 58.34± 11.9 | 0.01 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 41.6 | 0.30\* | 52.4 | 53.0 | 0.01 |
| Male | 38.6 | 55.9 | 0.35\* | 43.8 | 43.0 | 0.02 |
| Unknown | 4.9 | 2.5 | 0.13\* | 3.8 | 4.0 | 0.02 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 7.5 | 0.03 | 6.9 | 5.9 | 0.04 |
| Not Hispanic/Latinx | 75.6 | 70.9 | 0.11\* | 75.1 | 76.2 | 0.02 |
| Unknown | 17.7 | 21.6 | 0.09 | 18.0 | 17.9 | 0.002 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 1.0 | 0.03 | 0.9 | 1.0 | 0.01 |
| Black | 19.5 | 20.9 | 0.04 | 19.2 | 19.4 | 0.004 |
| White | 63.0 | 64.8 | 0.04 | 64.4 | 64.2 | 0.004 |
| Unknown | 12.2 | 9.1 | 0.10\* | 11.2 | 11.7 | 0.02 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 13.6 | 0.01 | 12.8 | 13.0 | 0.006 |
| **Problems related to lifestyle (%)** | 23.9 | 21.9 | 0.05 | 22.3 | 21.9 | 0.01 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 44.5 | 0.46\* | 58.9 | 60.8 | 0.04 |
| Severe obesity | 53.6 | 26.1 | 0.59\* | 44.0 | 43.5 | 0.01 |
| Depression | 62.8 | 51.8 | 0.22\* | 59.0 | 59.1 | 0.003 |
| Mood disorders | 70.4 | 59.5 | 0.23\* | 66.4 | 66.7 | 0.008 |
| Anxiety disorders | 69.1 | 57.1 | 0.25\* | 65.1 | 65.3 | 0.005 |
| Psychotic disorders | 6.9 | 10.3 | 0.13\* | 7.5 | 7.7 | 0.007 |
| Behavioral disorders | 21.3 | 11.8 | 0.26\* | 17.1 | 17.2 | 0.004 |
| Disorders of adult personality and behavior | 7.4 | 6.9 | 0.02 | 6.8 | 6.7 | 0.004 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 5.5 | 0.14\* | 8.2 | 8.4 | 0.007 |
| Chronic pain | 77.7 | 65.1 | 0.28\* | 73.4 | 73.5 | 0.004 |
| Alcohol use disorder | 13.9 | 19.2 | 0.14\* | 14.8 | 14.7 | 0.005 |
| Nicotine dependence | 44.4 | 49.7 | 0.11\* | 45.5 | 43.9 | 0.03 |
| Cannabis use disorder | 11.9 | 12.7 | 0.02 | 11.7 | 11.9 | 0.006 |
| Cocaine use disorder | 11.8 | 15.3 | 0.10\* | 11.9 | 12.5 | 0.02 |
| Other stimulant disorders | 8.1 | 8.4 | 0.009 | 7.3 | 8.2 | 0.03 |
| Other psychoactive substance related disorders | 22.6 | 26.6 | 0.09 | 22.8 | 23.2 | 0.009 |
| Drug overdose | 8.8 | 11.1 | 0.08 | 8.9 | 9.0 | 0.003 |
| Opioid overdose | 3.3 | 4.2 | 0.04 | 3.4 | 3.2 | 0.01 |
| Substance abuse treatment | 2.5 | 3.5 | 0.05 | 2.8 | 2.7 | 0.006 |
| Methadone | 10.2 | 12.6 | 0.08 | 10.9 | 10.1 | 0.03 |
| Buprenorphine | 13.9 | 10.5 | 0.10\* | 13.0 | 13.9 | 0.03 |
| Naltrexone | 3.6 | 1.7 | 0.12\* | 2.4 | 2.6 | 0.02 |
| Naloxone | 51.3 | 34.1 | 0.35\* | 46.5 | 47.3 | 0.02 |
| Opioid analgesics | 95.1 | 90.6 | 0.18\* | 94.2 | 94.5 | 0.01 |
| Sedatives/Hypontics | 82.9 | 74.9 | 0.20\* | 80.2 | 80.0 | 0.005 |
| Insulin | 63.2 | 63.6 | 0.009 | 63.5 | 62.9 | 0.01 |
| Metformin | 76.2 | 68.7 | 0.17\* | 74.5 | 74.6 | 0.001 |
| DPP-4i | 18.9 | 18.0 | 0.02 | 19.7 | 19.4 | 0.007 |
| SGLT2i | 23.8 | 7.4 | 0.46\* | 17.8 | 16.1 | 0.05 |
| SU | 33.1 | 41.2 | 0.17\* | 35.7 | 34.8 | 0.02 |
| TZD | 7.8 | 6.7 | 0.04 | 7.6 | 7.3 | 0.01 |
| Other GLP-1RAs | 32.1 | 9.0 | 0.60\* | 21.6 | 20.3 | 0.03 |
| Liraglutide | 16.6 | 4.4 | 0.41\* | 10.8 | 9.8 | 0.03 |
| Dulaglutide | 16.7 | 4.2 | 0.42\* | 11.7 | 10.3 | 0.05 |
| Exenatide | 5.5 | 2.2 | 0.17\* | 4.6 | 4.5 | 0.005 |
| Albiglutide | 0.6 | 0.2 | 0.07 | 0.5 | 0.5 | <.001 |
| Lixisenatide | 0.5 | 0.2 | 0.06 | 0.5 | 0.5 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 1.6 | 0.12\* | 2.5 | 2.9 | 0.02 |
| Hospitalizations | 62.5 | 65.1 | 0.06 | 61.8 | 61.3 | 0.01 |
| Emergency department visit | 70.4 | 64.9 | 0.12\* | 67.5 | 66.7 | 0.02 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

**Supplement Table 9**: Characteristics of the propensity-score matched semaglutide vs TZD groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **TZD** | **SMD** | **semaglutide** | **TZD** | **SMD** |
| **Total number** | 3,034 | 897 |  | 723 | 723 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 59.9± 11.3 | 0.23\* | 59.5 ± 10.7 | 59.1± 11.3 | 0.04 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 47.6 | 0.18\* | 49.5 | 49.8 | 0.006 |
| Male | 38.6 | 50.9 | 0.25\* | 48.1 | 48.5 | 0.008 |
| Unknown | 4.9 | 1.4 | 0.20\* | 2.4 | 1.7 | 0.05 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 12.3 | 0.19\* | 9.4 | 9.7 | 0.009 |
| Not Hispanic/Latinx | 75.6 | 71.6 | 0.09 | 74.7 | 74.4 | 0.006 |
| Unknown | 17.7 | 16.2 | 0.04 | 15.9 | 15.9 | <.001 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 1.2 | 0.05 | 1.4 | 1.4 | <.001 |
| Black | 19.5 | 18.2 | 0.03 | 19.2 | 17.8 | 0.04 |
| White | 63.0 | 69.6 | 0.14\* | 66.1 | 68.7 | 0.06 |
| Unknown | 12.2 | 6.6 | 0.19\* | 7.7 | 7.7 | <.001 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 12.6 | 0.04 | 12.3 | 12.9 | 0.02 |
| **Problems related to lifestyle (%)** | 23.9 | 23.0 | 0.03 | 21.2 | 22.8 | 0.04 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 46.9 | 0.40\* | 50.2 | 49.5 | 0.01 |
| Severe obesity | 53.6 | 27.0 | 0.56\* | 32.1 | 32.0 | 0.003 |
| Depression | 62.8 | 52.7 | 0.21\* | 53.9 | 54.8 | 0.02 |
| Mood disorders | 70.4 | 61.8 | 0.18\* | 62.4 | 63.2 | 0.02 |
| Anxiety disorders | 69.1 | 59.3 | 0.21\* | 62.1 | 60.9 | 0.03 |
| Psychotic disorders | 6.9 | 8.7 | 0.07 | 8.6 | 7.9 | 0.03 |
| Behavioral disorders | 21.3 | 15.6 | 0.15\* | 15.6 | 16.3 | 0.02 |
| Disorders of adult personality and behavior | 7.4 | 6.2 | 0.05 | 5.9 | 5.9 | <.001 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 4.6 | 0.18\* | 5.3 | 5.3 | <.001 |
| Chronic pain | 77.7 | 67.3 | 0.23\* | 69.0 | 70.3 | 0.03 |
| Alcohol use disorder | 13.9 | 14.8 | 0.03 | 13.0 | 14.2 | 0.04 |
| Nicotine dependence | 44.4 | 44.0 | 0.007 | 42.3 | 44.0 | 0.03 |
| Cannabis use disorder | 11.9 | 10.9 | 0.03 | 9.5 | 11.6 | 0.07 |
| Cocaine use disorder | 11.8 | 10.9 | 0.03 | 9.7 | 9.8 | 0.005 |
| Other stimulant disorders | 8.1 | 8.4 | 0.009 | 7.1 | 6.9 | 0.005 |
| Other psychoactive substance related disorders | 22.6 | 20.7 | 0.05 | 20.6 | 20.1 | 0.01 |
| Drug overdose | 8.8 | 8.6 | 0.007 | 7.5 | 8.2 | 0.03 |
| Opioid overdose | 3.3 | 4.1 | 0.04 | 3.7 | 3.7 | <.001 |
| Substance abuse treatment | 2.5 | 1.8 | 0.05 | 2.8 | 2.7 | 0.006 |
| Methadone | 10.2 | 9.9 | 0.008 | 10.4 | 9.8 | 0.02 |
| Buprenorphine | 13.9 | 11.6 | 0.07 | 12.2 | 12.7 | 0.02 |
| Naltrexone | 3.6 | 1.1 | 0.16\* | 1.4 | 1.4 | <.001 |
| Naloxone | 51.3 | 35.6 | 0.32\* | 38.3 | 40.4 | 0.04 |
| Opioid analgesics | 95.1 | 91.6 | 0.14\* | 92.8 | 92.5 | 0.01 |
| Sedatives/Hypontics | 82.9 | 76.9 | 0.15\* | 79.1 | 78.3 | 0.02 |
| Insulin | 63.2 | 62.7 | 0.01 | 65.8 | 62.9 | 0.06 |
| Metformin | 76.2 | 71.9 | 0.09 | 73.2 | 73.4 | 0.006 |
| DPP-4i | 18.9 | 27.4 | 0.20\* | 25.9 | 26.6 | 0.02 |
| SGLT2i | 23.8 | 18.1 | 0.14\* | 21.9 | 20.2 | 0.04 |
| SU | 33.1 | 49.1 | 0.33\* | 47.7 | 45.1 | 0.05 |
| TZD | 7.8 | 28.1 | 0.55\* | 20.6 | 19.5 | 0.03 |
| Other GLP-1RAs | 32.1 | 18.1 | 0.33\* | 21.2 | 20.1 | 0.03 |
| Liraglutide | 16.6 | 7.0 | 0.30\* | 8.6 | 7.7 | 0.03 |
| Dulaglutide | 16.7 | 9.0 | 0.23\* | 11.2 | 10.8 | 0.01 |
| Exenatide | 5.5 | 5.8 | 0.01 | 5.9 | 5.7 | 0.01 |
| Albiglutide | 0.6 | 1.1 | 0.05 | 1.4 | 1.4 | <.001 |
| Lixisenatide | 0.5 | 1.1 | 0.07 | 1.4 | 1.4 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 2.8 | 0.05 | 2.8 | 2.5 | 0.02 |
| Hospitalizations | 62.5 | 59.1 | 0.07 | 57.0 | 58.8 | 0.04 |
| Emergency department visit | 70.4 | 63.0 | 0.16\* | 63.8 | 62.9 | 0.02 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

**Supplement Table 10**: Characteristics of the propensity-score matched semaglutide vs other GLP-1RAs groups before and after propensity-score matching for baseline covariates for the study population of patients with comorbid T2DM and OUD.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Before propensity-score matching** | | | **After propensity-score matching** | | |
| **semaglutide** | **Other GLP-1 RAs** | **SMD** | **semaglutide** | **Other GLP-1 RAs** | **SMD** |
| **Total number** | 3,034 | 4,886 |  | 2,406 | 2,406 |  |
| **Age at index event (years, mean±SD)** | 57.4 ± 11.0 | 57.2 ± 11.0 | 0.02 | 57.5 ± 11.0 | 57.4± 11.2 | 0.01 |
| **Sex (%)** |  |  |  |  |  |  |
| Female | 56.5 | 50.0 | 0.13\* | 54.8 | 54.7 | 0.002 |
| Male | 38.6 | 47.8 | 0.19\* | 41.5 | 41.6 | 0.003 |
| Unknown | 4.9 | 2.2 | 0.15\* | 3.7 | 3.6 | 0.002 |
| **Ethnicity (%)** |  |  |  |  |  |  |
| Hispanic/Latinx | 6.7 | 9.9 | 0.12\* | 7.4 | 7.0 | 0.02 |
| Not Hispanic/Latinx | 75.6 | 69.9 | 0.13\* | 74.5 | 74.9 | 0.009 |
| Unknown | 17.7 | 20.3 | 0.04 | 18.0 | 18.1 | 0.001 |
| **Race (%)** |  |  |  |  |  |  |
| Asian | 0.7 | 0.9 | 0.02 | 0.9 | 0.8 | 0.009 |
| Black | 19.5 | 22.9 | 0.08 | 20.1 | 19.7 | 0.01 |
| White | 63.0 | 60.2 | 0.06 | 62.3 | 63.8 | 0.03 |
| Unknown | 12.2 | 10.9 | 0.04 | 11.6 | 11.2 | 0.01 |
| **Adverse socioeconomic determinants of health (%)** | 14.0 | 14.5 | 0.01 | 13.6 | 13.8 | 0.005 |
| **Problems related to lifestyle (%)** | 23.9 | 26.4 | 0.06 | 23.6 | 23.0 | 0.02 |
| **Pre-existing medical conditions, procedures, medications (%)** |  |  |  |  |  |  |
| Obesity | 66.5 | 59.3 | 0.15\* | 63.5 | 64.0 | 0.01 |
| Severe obesity | 53.6 | 41.9 | 0.24\* | 50.3 | 51.5 | 0.02 |
| Depression | 62.8 | 60.3 | 0.05 | 61.9 | 61.4 | 0.01 |
| Mood disorders | 70.4 | 69.0 | 0.03 | 69.5 | 69.4 | 0.003 |
| Anxiety disorders | 69.1 | 65.7 | 0.07 | 68.0 | 68.4 | 0.009 |
| Psychotic disorders | 6.9 | 9.9 | 0.11\* | 7.5 | 7.6 | 0.003 |
| Behavioral disorders | 21.3 | 17.0 | 0.11\* | 19.9 | 19.5 | 0.008 |
| Disorders of adult personality and behavior | 7.4 | 7.6 | 0.006 | 7.4 | 7.8 | 0.02 |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence | 9.1 | 7.2 | 0.07 | 8.1 | 8.4 | 0.01 |
| Chronic pain | 77.7 | 71.6 | 0.14\* | 75.8 | 74.9 | 0.02 |
| Alcohol use disorder | 13.9 | 18.5 | 0.13\* | 14.3 | 15.4 | 0.03 |
| Nicotine dependence | 44.4 | 51.2 | 0.14\* | 46.1 | 45.7 | 0.008 |
| Cannabis use disorder | 11.9 | 12.4 | 0.02 | 11.7 | 11.9 | 0.006 |
| Cocaine use disorder | 11.8 | 15.4 | 0.11\* | 11.8 | 12.2 | 0.01 |
| Other stimulant disorders | 8.1 | 7.6 | 0.02 | 7.5 | 7.3 | 0.006 |
| Other psychoactive substance related disorders | 22.6 | 27.1 | 0.10\* | 22.7 | 23.6 | 0.02 |
| Drug overdose | 8.8 | 11.3 | 0.08 | 9.3 | 9.1 | 0.006 |
| Opioid overdose | 3.3 | 4.5 | 0.06 | 3.5 | 3.4 | 0.005 |
| Substance abuse treatment | 2.5 | 2.0 | 0.04 | 2.2 | 2.5 | 0.01 |
| Methadone | 10.2 | 13.5 | 0.10\* | 11.0 | 10.6 | 0.01 |
| Buprenorphine | 13.9 | 14.4 | 0.02 | 13.8 | 14.2 | 0.01 |
| Naltrexone | 3.6 | 2.6 | 0.06 | 2.7 | 3.2 | 0.03 |
| Naloxone | 51.3 | 44.5 | 0.14\* | 49.0 | 49.3 | 0.006 |
| Opioid analgesics | 95.1 | 93.5 | 0.07 | 94.8 | 94.4 | 0.02 |
| Sedatives/Hypontics | 82.9 | 80.2 | 0.07 | 82.0 | 82.2 | 0.004 |
| Insulin | 63.2 | 74.3 | 0.24\* | 66.3 | 65.2 | 0.02 |
| Metformin | 76.2 | 76.2 | <.001 | 75.9 | 76.1 | 0.006 |
| DPP-4i | 18.9 | 21.6 | 0.07 | 19.6 | 19.6 | <.001 |
| SGLT2i | 23.8 | 17.0 | 0.17\* | 21.4 | 21.0 | 0.01 |
| SU | 33.1 | 38.4 | 0.11\* | 34.4 | 34.2 | 0.003 |
| TZD | 7.8 | 7.9 | 0.003 | 7.8 | 8.2 | 0.02 |
| Other GLP-1RAs | 32.1 | 15.3 | 0.40\* | 22.4 | 22.3 | 0.003 |
| Liraglutide | 16.6 | 9.2 | 0.22\* | 13.2 | 13.3 | 0.001 |
| Dulaglutide | 16.7 | 4.3 | 0.41\* | 9.0 | 8.2 | 0.03 |
| Exenatide | 5.5 | 4.6 | 0.04 | 5.8 | 5.4 | 0.01 |
| Albiglutide | 0.6 | 0.4 | 0.04 | 0.7 | 0.6 | 0.01 |
| Lixisenatide | 0.5 | 0.2 | 0.05 | 0.4 | 0.4 | <.001 |
| Other blood glucose lowering drugs, excl. insulins | 3.6 | 2.4 | 0.07 | 2.9 | 3.2 | 0.02 |
| Hospitalizations | 62.5 | 65.8 | 0.07 | 62.9 | 62.1 | 0.02 |
| Emergency department visit | 70.4 | 71.4 | 0.02 | 69.6 | 69.7 | 0.003 |

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized mean differences. \*SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (Z55-Z65) include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (Z72) included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for “adverse socioeconomic determinants of health" and "problems related to lifestyle", the parent codes (Z55-Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.”

# **Supplement Figure 2**. Comparison of risk and hazard rate of negative control outcome in patients with comorbid T2DM and OUD between propensity-score matched semaglutide and other anti-diabetes medications groups.

Outcomes were followed for 1 year after the index event for both exposure and comparison groups. Hazard rates were calculated using a Cox proportional hazards model with censoring applied. Overall risk = the number of patients with outcomes during the follow-up time window/number of patients in the cohort at the beginning of the time window.

T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

# Reference

1. Vivolo-Kantor, A. *et al.* Defining indicators for drug overdose emergency department visits and hospitalisations in ICD-10-CM coded discharge data. *Inj. Prev.* **27**, i56–i61 (2021).