Supplement Results

**Semaglutide and opioid overdose risk in patients with type 2 diabetes and opioid use disorder**

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# **Supplement Results Table 1**: 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 ResultsTable 2**: 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 Results Table 3**: 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 Results Table 4**: 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 Results Table 5**: 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 Results Table 6**: 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 Results Figure 1**. Cumulative instances, comparing propensity-score matched semaglutide and other antidiabetic medications groups in patients with comorbid T2DM and OUD.



Each eligible patient was followed from the index event until the occurrence of the outcome, death, loss to follow-up, or 1 year after the index event, whichever occurred first. Hazard rates were calculated using a Cox proportional hazards model, and cumulative instances were calculated using Kaplan-Meier Survival analysis, 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.

The average follow-up times for semaglutide vs. each comparison group are as follows: insulin (342.0 ± 21.0 vs. 329.0 ± 32.7 days), metformin (342.5 ± 20.6 vs. 337.6 ± 25.5 days), DPP-4i (342.1 ± 20.9 vs. 329.4 ± 32.1 days), SGLT2i (341.8 ± 21.1 vs. 332.1 ± 29.8 days), SU (341.7 ± 21.3 vs. 335.6 ± 27.0 days), TZD (353.5 ± 10.5 vs. 330.6 ± 31.3 days), other GLP-1RAs (342.7 ± 20.4 vs. 340.6 ± 22.6 days), liraglutide (341.6 ± 21.4 vs. 339.7 ± 23.5 days), and dulaglutide (342.6 ± 20.5 vs. 340.4 ± 22.7 days).

# **Supplement Results 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.