

Supplement Results

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

William Wang¹, Nora D. Volkow^{2*}, MD, QuangQiu Wang³, Nathan A. Berger¹, MD, Pamela B Davis⁴, MD, PhD, David C. Kaelber⁵, MD, PhD, MPH, Rong Xu^{3*}, PhD

¹Center for Science, Health, and Society, Case Western Reserve University School of Medicine, Cleveland, OH, USA

²National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA

³Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, OH, USA

⁴Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, OH, USA

⁵Center for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, OH, USA

Table of Contents

<i>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.</i>	3
<i>Supplement Results Table 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</i>	5
<i>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.</i>	8
<i>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.</i>	10
<i>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</i>	13
<i>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</i>	15
<i>Supplement Results Figure 1. Cumulative instances, comparing propensity-score matched semaglutide and other antidiabetic medications groups in patients with comorbid T2DM and OUD.</i>	18
<i>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.</i>	23

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/Hypnotics	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/Hypnotics	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/Hypnotics	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/Hypnotics	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/Hypnotics	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.

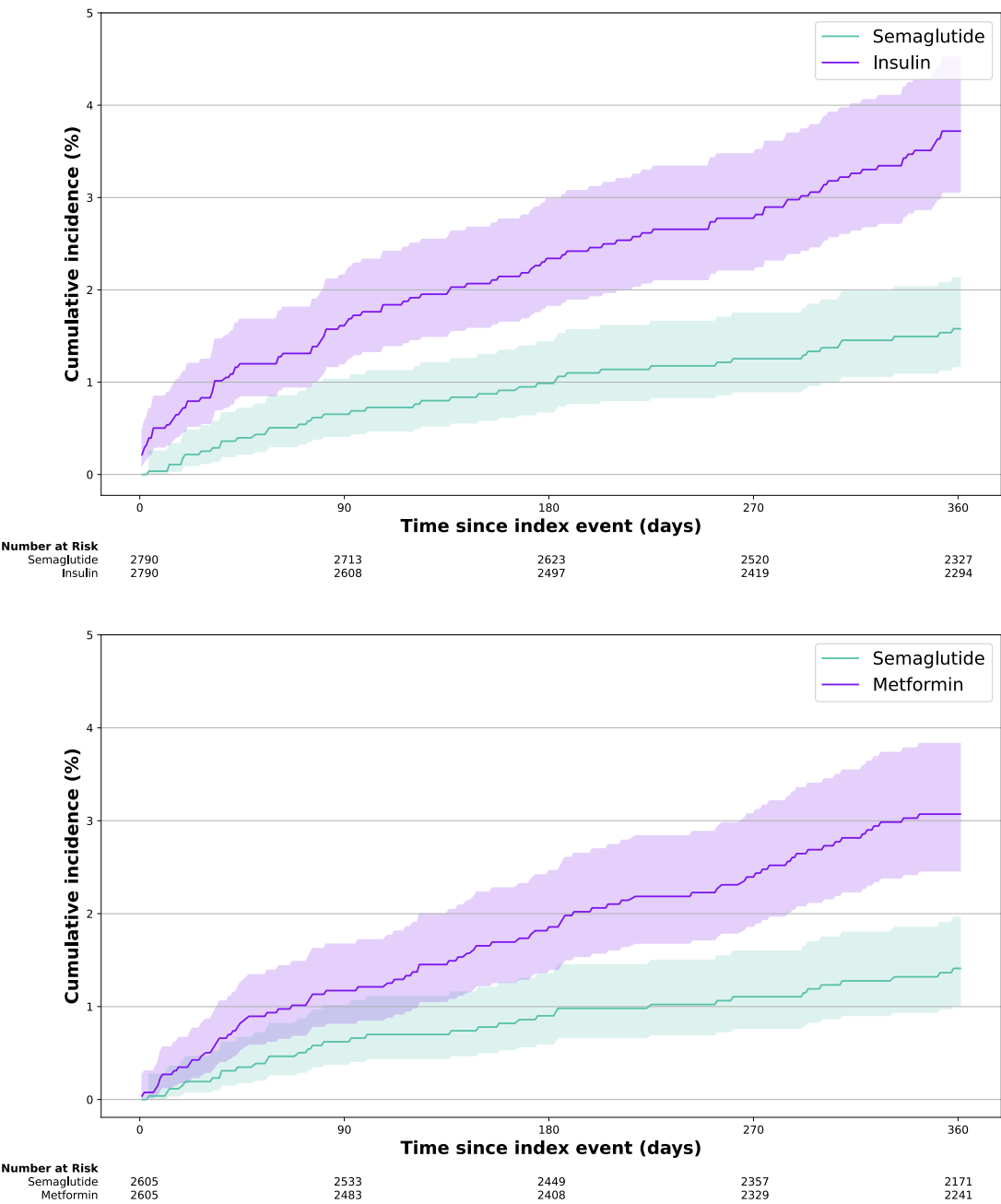
	Before propensity-score matching			After propensity-score matching		
	semaglutide	Other GLP-1 RAs	SMD	semaglutide	Other GLP-1 RAs	SMD
Total number	3,034	4,886		2,406	2,406	
Age at index event (years, mean±SD)	57.4 ± 11.0	57.2 ± 11.0	0.02	57.5 ± 11.0	57.4± 11.2	0.01
Sex (%)						
Female	56.5	50.0	0.13*	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 (%)						

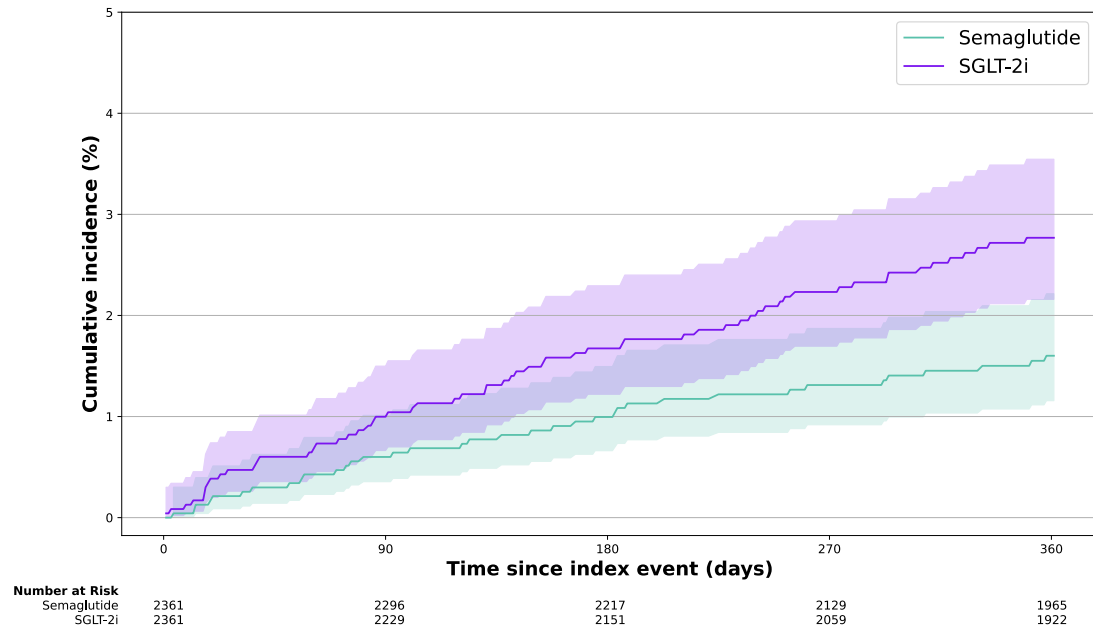
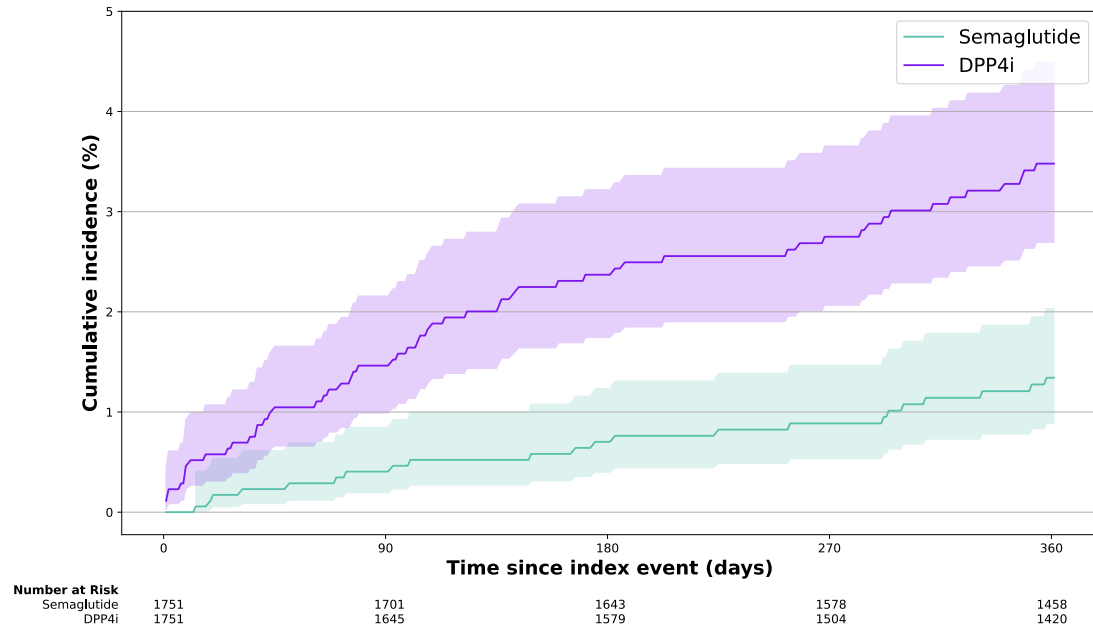
Asian	0.7	0.9	0.02	0.9	0.8	0.009
Black	19.5	22.9	0.08	20.1	19.7	0.01
White	63.0	60.2	0.06	62.3	63.8	0.03
Unknown	12.2	10.9	0.04	11.6	11.2	0.01
Adverse socioeconomic determinants of health (%)	14.0	14.5	0.01	13.6	13.8	0.005
Problems related to lifestyle (%)	23.9	26.4	0.06	23.6	23.0	0.02
Pre-existing medical 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

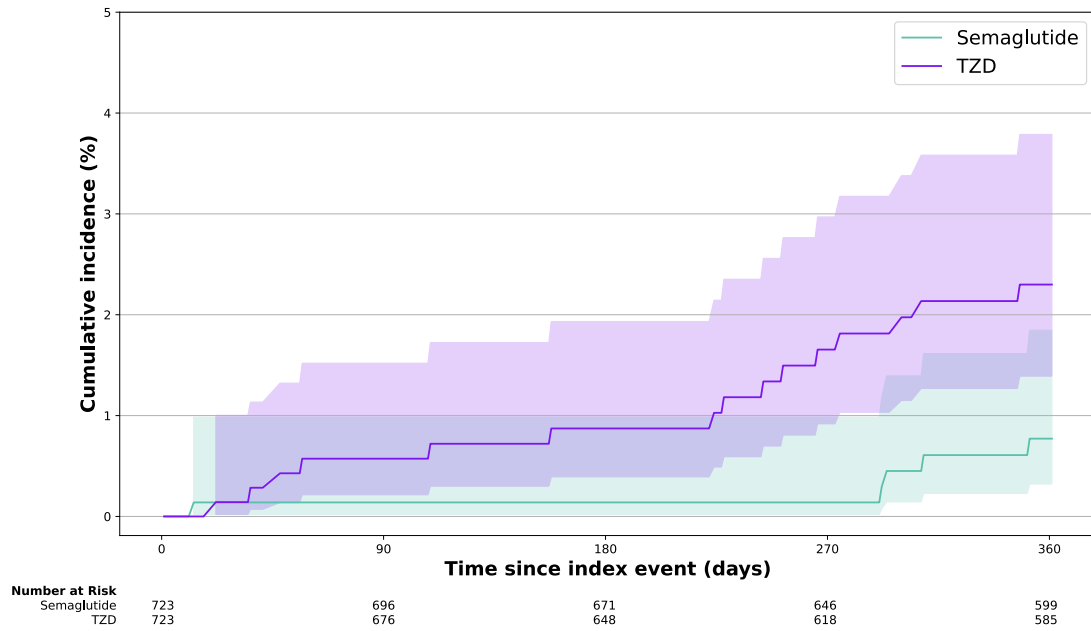
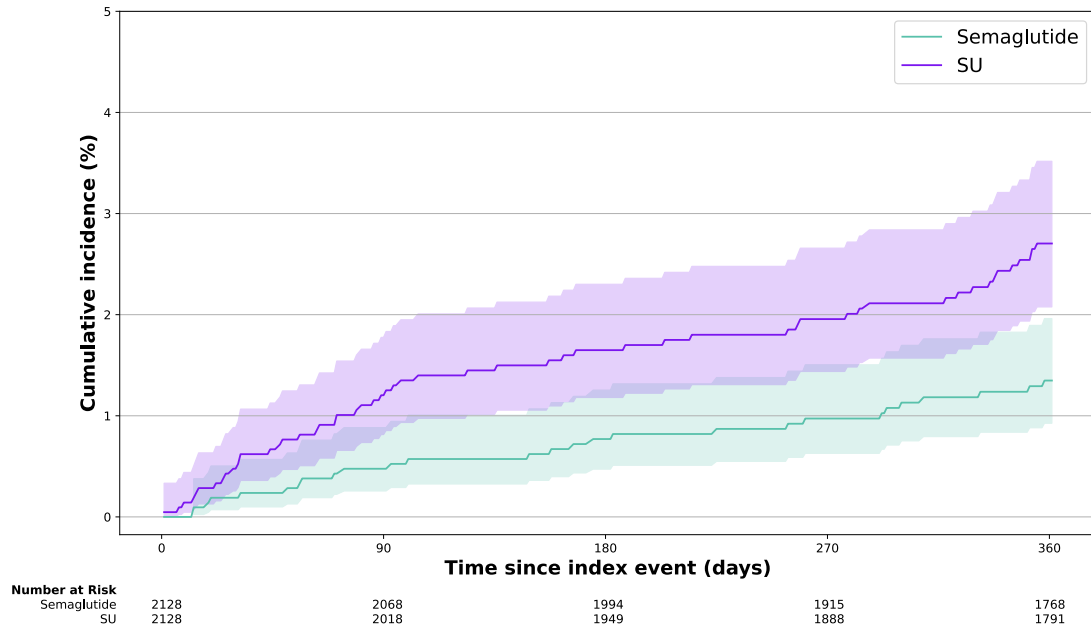
Other psychoactive substance related disorders	22.6	27.1	0.10*	22.7	23.6	0.02
Drug overdose	8.8	11.3	0.08	9.3	9.1	0.006
Opioid overdose	3.3	4.5	0.06	3.5	3.4	0.005
Substance abuse treatment	2.5	2.0	0.04	2.2	2.5	0.01
Methadone	10.2	13.5	0.10*	11.0	10.6	0.01
Buprenorphine	13.9	14.4	0.02	13.8	14.2	0.01
Naltrexone	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/Hypnotics	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

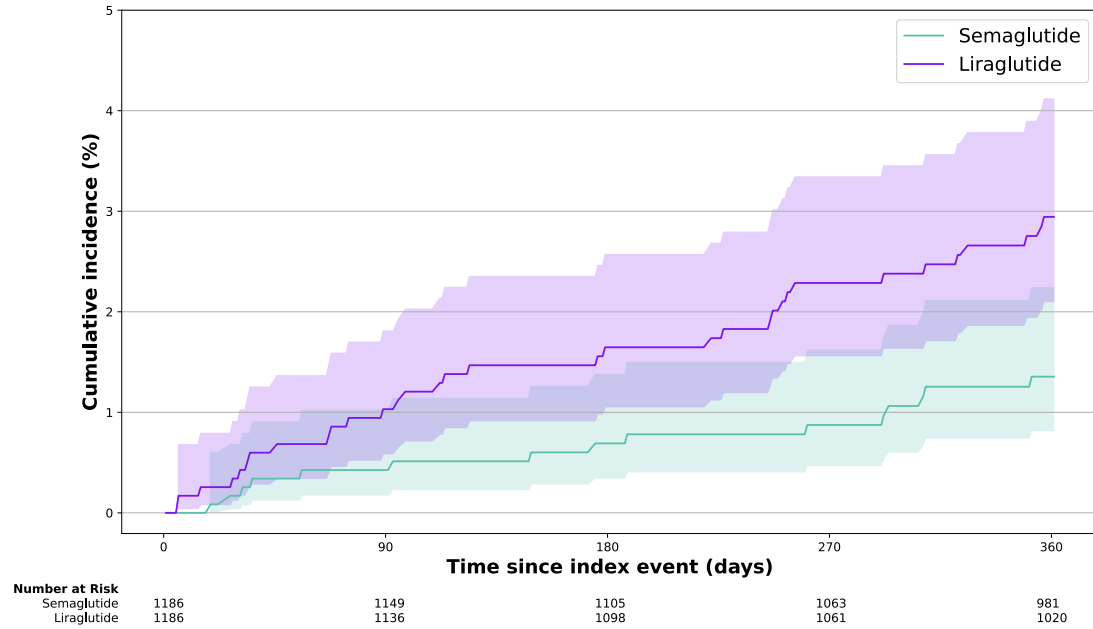
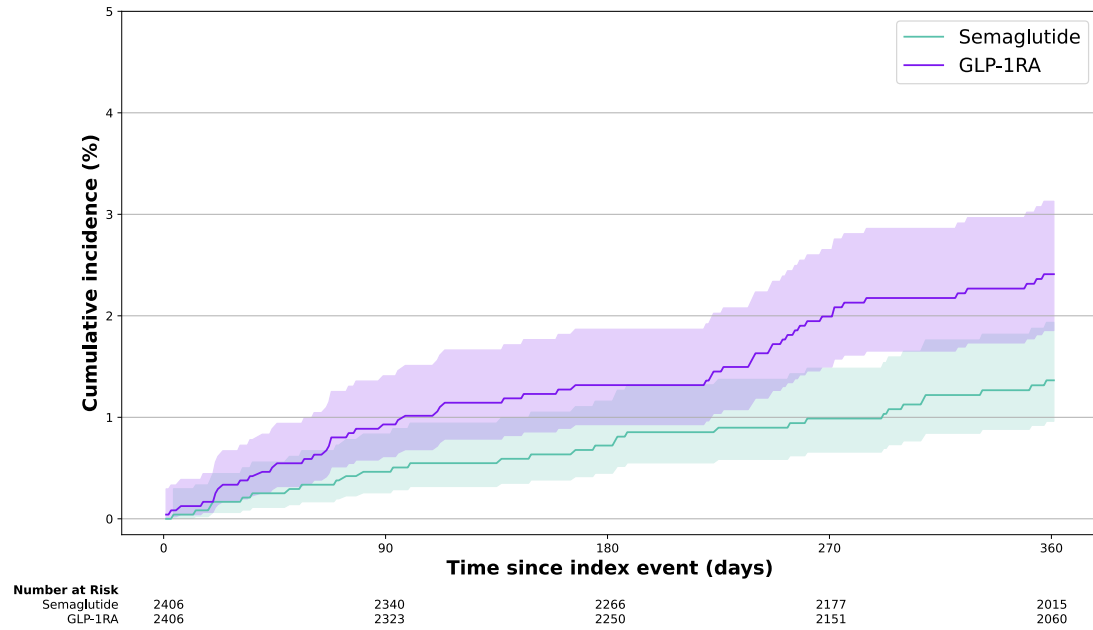
T2DM – Type 2 diabetes; OUD – Opioid use disorder; DPP-4i – Dipeptidyl-peptidase-4 inhibitors; SGLT2i – Sodium-glucose cotransporter-2 inhibitors; SU – Sulfonylureas, TZD – Thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. SMD – standardized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

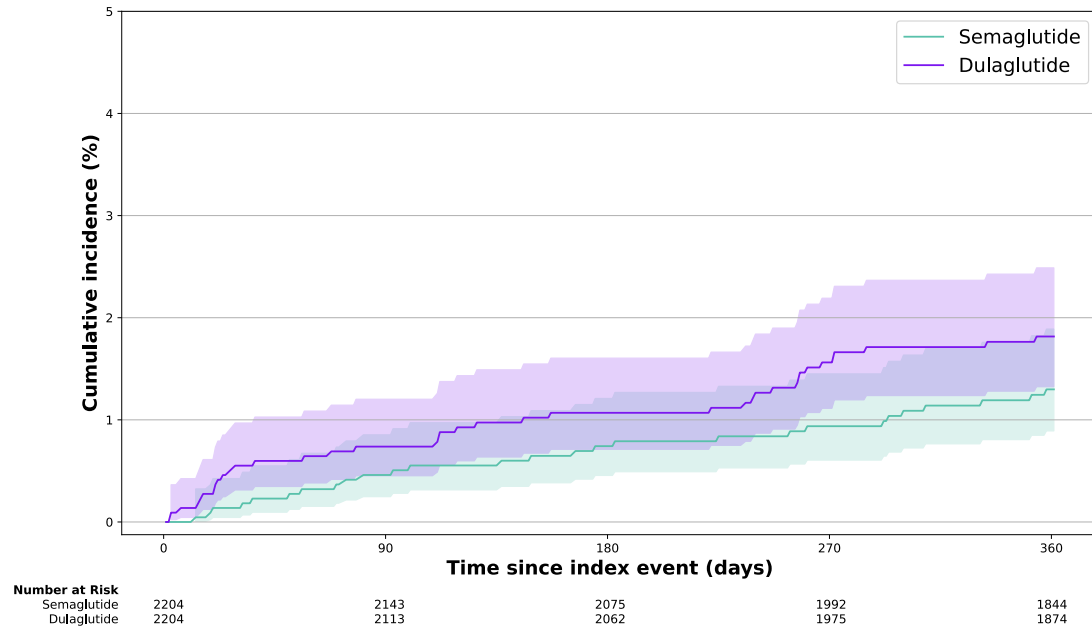
Supplement Results Figure 1. Cumulative instances, comparing propensity-score matched semaglutide and other antidiabetic medications groups in patients with comorbid T2DM and OUD.









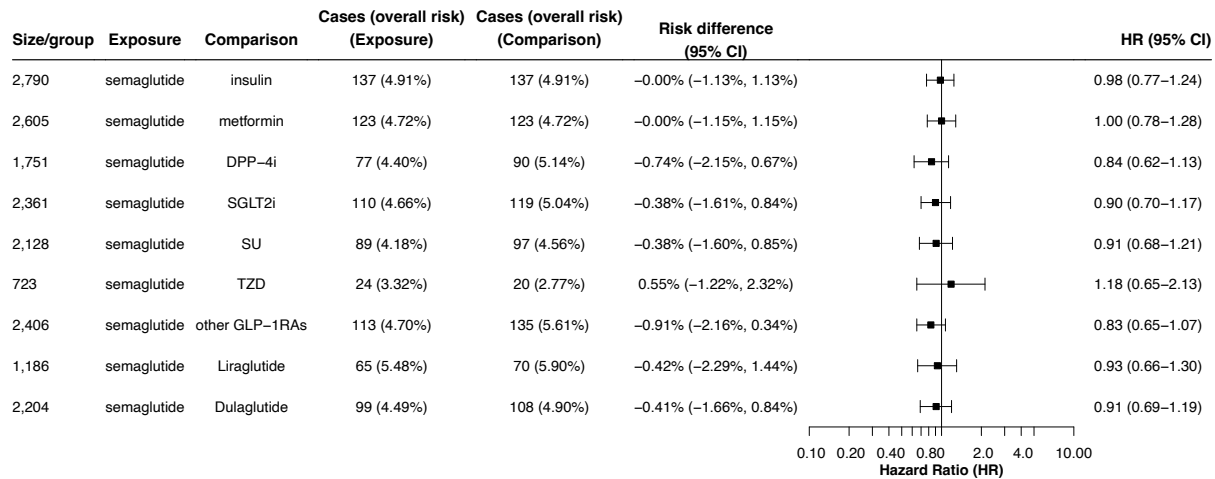


Each eligible patient was followed from the index event until the occurrence of the outcome, death, loss to follow-up, or 1 year after the index event, whichever occurred first. Hazard rates were calculated using a Cox proportional hazards model, and cumulative instances were calculated using Kaplan-Meier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

**12 month risk of medical encounters for congenital malformations, deformations, and chromosomal abnormalities
in patients with comorbid T2DM and OUD
(Comparison between matched semaglutide vs 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.