Semaglutide and substance use disorders: real-world evidence

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National Academies: Examining Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists for Central Nervous System Disorders: A Workshop

September 10, Washington DC

Conflict of Interest

None

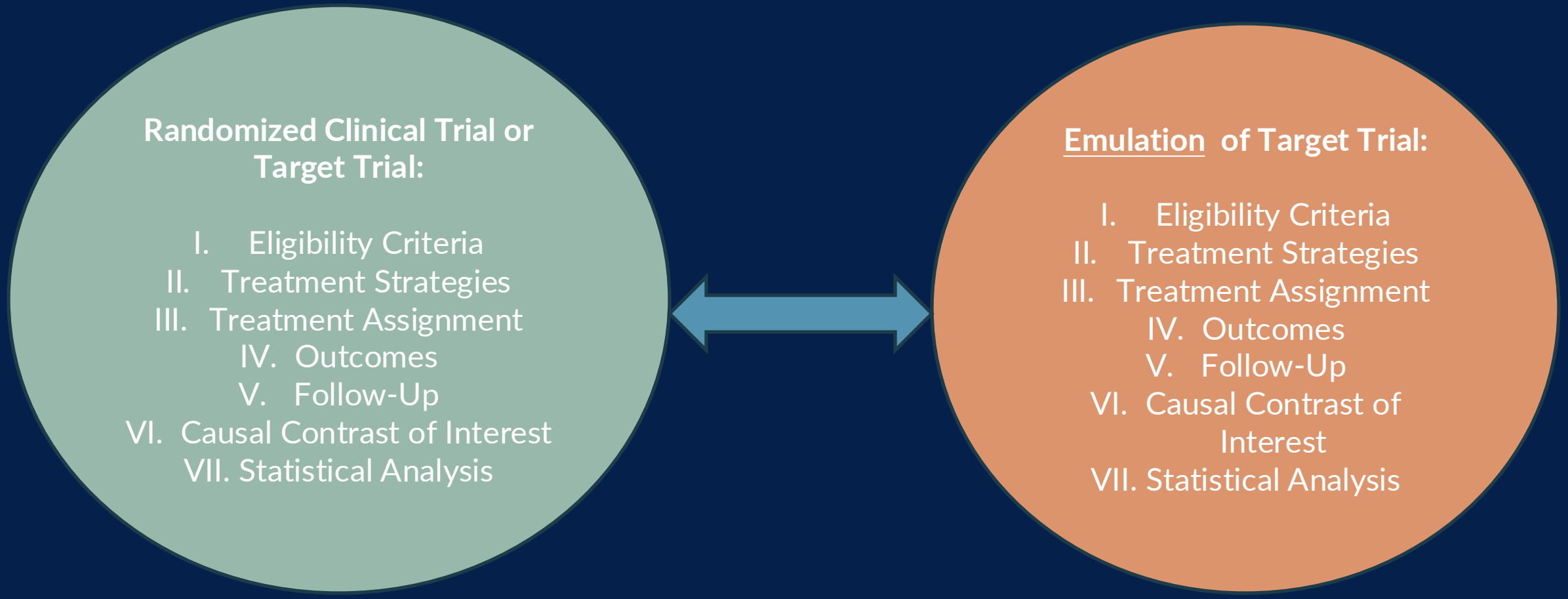
Longitudinal Real-world patient EHRs

TriNetX: a global network of healthcare organizations and life science companies driving real-world research

Our study focused on the *US* population:

- **D**e-identified electronic health records of 117 million unique patients from the TriNetX Network platform, 66 healthcare organizations in the US
- Data elements: demographics, SDOHs, Lifestyles, diagnosis, medications, lab tests, procedures, genomics
- Mortality data: social security index, obituary
- >20 years history

Target trial emulation using real-world data



Trial Participants (hundreds)
Cost: $ 10-50 million

Real-World Patients (millions)
Cost: $ <1 million

Semaglutide and alcohol use disorder (AUD)

nature communications

Article

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Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population

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Alcohol use disorders are among the top causes of the global burden of disease, yet therapeutic interventions are limited. Reduced desire to drink in patients treated with semaglutide has raised interest regarding its potential therapeutic benefits for alcohol use disorders. In this retrospective cohort study of electronic health records of 83,825 patients with obesity, we show that semaglutide compared with other anti-obesity medications is associated with a 50%-56% lower risk for both the incidence and recurrence of alcohol use disorder for a 12-month follow-up period. Consistent reductions were seen for patients stratified by gender, age group, race and in patients with and without type 2 diabetes. Similar findings are replicated in the study population with 598,803 patients with type 2 diabetes. These findings provide evidence of the potential benefit of semaglutide in AUD in real-world populations and call for further randomized clinical trials.

Semaglutide and AUD: 4 emulation target trials

Trial #1 (*AUD incidence*):

- **83,825 patients** with obesity and ***no prior AUD***
- **Treatment strategy**: Semaglutide (Wegovy) vs. other weight loss drugs
- **Cohort matching**: propensity-score matching for baseline characteristics
- **Outcome**: first-time AUD diagnosis
- **Follow-up**: 12-month

Trial #2 (*AUD incidence*):

- **598,803 patients** with type 2 diabetes and ***no prior AUD***
- **Treatment strategies:** Semaglutide (Ozempic) *vs.* other anti-diabetic drugs
- **Cohort matching**: propensity-score matching for baseline characteristics
- **Outcome:** first-time AUD diagnosis
- **Follow-up**: 12-month

Trial #3 (*AUD recurrence*):

- **4,254 patients** with obesity and ***pre-existing AUD***
- **Treatment strategy:** Semaglutide (Wegovy) vs. other weight loss drugs
- **Cohort matching:** propensity-score matching for baseline characteristics
- **Outcome:** subsequent medical encounter for AUD diagnosis
- **Follow-up:** 12-month

Trial #4 (*AUD recurrence*):

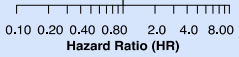
- **22,113 patients** with type 2 diabetes and ***pre-existing AUD***
- **Treatment strategies:** Semaglutide (Ozempic) *vs.* other anti-diabetes drugs
- **Cohort matching**: propensity-score matching for baseline characteristics
- **Outcome:** subsequent medical encounter for AUD diagnosis
- **Follow-up**: 12-month

Semaglutide (Wegovy) and reduced incident and recurrent AUD in patients with obesity

Incident AUD diagnosis: 50% reduction

Incident AUD diagnosis in patients with obesity and no prior history of AUD during 12–month follow–up time period (comparison between propensity–score matched cohorts)

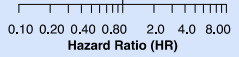
Population	semaglutide cohort	non–GLP–1RA anti–obesity medications cohort	HR (95% CI)
Overall (n = 26,566/cohort)	0.37% (98)	0.73% (193)	0.50 (0.39–0.63)
Women (n = 17,977/cohort)	0.22% (40)	0.44% (79)	0.50 (0.34–0.73)
Men (n = 6,903/cohort)	0.59% (41)	1.14% (79)	0.50 (0.35–0.74)
age <= 55 years (n = 15,767/cohort)	0.30% (48)	0.61% (96)	0.49 (0.35–0.70)
age > 55 years (n = 10,440/cohort)	0.48% (50)	0.86% (90)	0.54 (0.38–0.76)
Black (n = 4,107/cohort)	0.32% (13)	0.71% (29)	0.43 (0.23–0.83)
White (n = 17,861/cohort)	0.35% (62)	0.67% (120)	0.51 (0.38–0.69)
No T2DM (n = 17,609/cohort)	0.39% (68)	0.60% (106)	0.64 (0.47–0.87)
T2DM (n = 8,696/cohort)	0.30% (26)	0.90% (78)	0.32 (0.20–0.49)



Recurrent AUD diagnosis: 56% reduction

Recurrent AUD diagnosis in patients with obesity and a prior history of AUD during 12–month follow–up time period (comparison between propensity–score matched cohorts)

Population	semaglutide cohort	non–GLP–1RA anti–obesity medications cohort	HR (95% CI)
Overall (n = 1,051/cohort)	22.6% (238)	43.0% (452)	0.44 (0.38–0.52)
Women (n = 420/cohort)	19.0% (80)	32.9% (138)	0.51 (0.39–0.67)
Men (n = 553/cohort)	23.9% (132)	46.5% (257)	0.42 (0.34–0.51)
age <= 55 years (n = 586/cohort)	22.9% (134)	43.9% (257)	0.44 (0.35–0.54)
age > 55 years (n = 440/cohort)	23.2% (102)	36.8% (162)	0.55 (0.43–0.70)
Black (n = 140/cohort)	20.7% (29)	37.1% (52)	0.49 (0.31–0.78)
White (n = 699/cohort)	22.7% (159)	41.5% (290)	0.46 (0.38–0.56)
No T2D (n = 540/cohort)	20.6% (111)	41.5% (224)	0.42 (0.33–0.52)
T2D (n = 453/cohort)	24.3% (110)	40.4% (183)	0.50 (0.39–0.63)



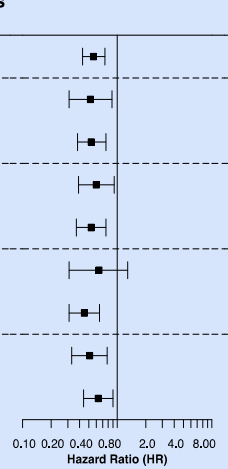
Semaglutide (Ozempic) and reduced incident and recurrent AUD in patients with type 2 diabetes

Incident AUD diagnosis: 44% reduction

Recurrent AUD diagnosis: 40% reduction

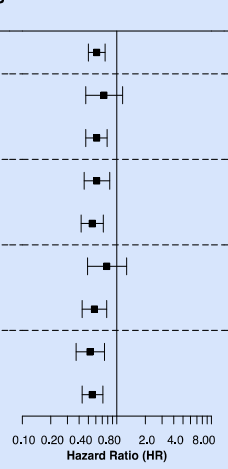
Incident AUD diagnosis in patients with T2DM and no prior history of AUD during 12–month follow–up time period (comparison between propensity–score matched cohorts)

Population	semaglutide cohort	non–GLP–1RA anti–diabetes medications cohort	HR (95% CI)
Overall (n = 25,670/cohort)	0.32% (81)	0.52% (134)	0.56 (0.43–0.74)
Women (n = 11,743/cohort)	0.19% (22)	0.34% (40)	0.52 (0.31–0.88)
Men (n = 11,833/cohort)	0.41% (49)	0.73% (86)	0.53 (0.38–0.76)
age <= 55 years (n = 9,974/cohort)	0.34% (34)	0.53% (53)	0.60 (0.39–0.93)
age > 55 years (n = 15,951/cohort)	0.30% (47)	0.53% (84)	0.53 (0.37–0.76)
Black (n = 3,752/cohort)	0.35% (13)	0.51% (19)	0.64 (0.31–1.29)
White (n = 15,452/cohort)	0.28% (43)	0.58% (90)	0.45 (0.31–0.65)
No obesity (n = 10,112/cohort)	0.33% (33)	0.58% (59)	0.51 (0.33–0.78)
Obesity (n = 15,551/cohort)	0.31% (48)	0.47% (73)	0.63 (0.44–0.90)



Recurrent AUD diagnosis in patients with T2DM and a prior history of AUD during 12–month follow–up time period (comparison between propensity–score matched cohorts)

Population	semaglutide cohort	non–GLP–1RA anti–diabetes medications cohort	HR (95% CI)
Overall (n = 653/cohort)	23.4% (153)	33.2% (217)	0.61 (0.50–0.75)
Women (n = 163/cohort)	20.9% (34)	26.4% (43)	0.73 (0.47–1.15)
Men (n = 443/cohort)	22.1% (98)	31.2% (138)	0.61 (0.47–0.79)
age <= 55 years (n = 258/cohort)	26.7% (69)	37.6% (97)	0.61 (0.45–0.84)
age > 55 years (n = 402/cohort)	20.6% (83)	32.8% (132)	0.55 (0.42–0.72)
Black (n = 104/cohort)	29.8% (31)	34.6% (36)	0.78 (0.49–1.27)
White (n = 370/cohort)	19.7% (73)	29.7% (110)	0.58 (0.43–0.78)
No obesity (n = 195/cohort)	26.2% (51)	41.5% (81)	0.52 (0.37–0.74)
Obesity (n = 463/cohort)	21.2% (98)	33.3% (154)	0.55 (0.43–0.71)



Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R*. Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. Nature Communications 2024.*

Semaglutide and cannabis use disorder (CUD)

Molecular Psychiatry www.nature.com/mp

IMMEDIATE COMMUNICATION OPEN

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Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study

William Wang[1], Nora D. Volkow[2]✉, Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] and Rong Xu[5]✉

Cannabis is the most frequently used illicit drug in the United States with more than 45 million users of whom one-third suffer from a cannabis use disorder (CUD). Despite its high prevalence, there are currently no FDA-approved medications for CUD. Patients treated with semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for treating type 2 diabetes (T2D) and for weight management have reported reduced desire to drink and smoke. Preclinical studies have shown that semaglutide decreased nicotine and alcohol consumption. Preclinical and preliminary clinical evidence of semaglutide's potential beneficial effects on various substance use disorders led us to evaluate if it pertained to CUD. In this retrospective cohort study of electronic health records (EHRs) from the TriNetX Analytics Network, a global federated health research network of approximately 105.3 million patients from 61 large healthcare organizations in the US, we aimed to assess the associations of semaglutide with both incident and recurrent CUD diagnosis compared to non-GLP-1RA anti-obesity or anti-diabetes medications. Hazard ratio (HR) and 95% confidence intervals (CI) of incident and recurrent CUD were calculated for 12-month follow-up by comparing propensity-score matched patient cohorts. The study population included 85,223 patients with obesity who were prescribed semaglutide or non-GLP-1RA anti-obesity medications, with the findings replicated in 596,045 patients with T2D. In patients with obesity (mean age 51.3 years, 65.6% women), semaglutide compared with non-GLP-1RA anti-obesity medications was associated with lower risk for incident CUD in patients with no prior history CUD (HR: 0.56, 95% CI: 0.42–0.75), and recurrent CUD diagnosis in patients with a prior history CUD (HR: 0.62, 95% CI: 0.46–0.84). Consistent reductions were seen for patients stratified by gender, age group, race and in patients with and without T2D. Similar findings were replicated in the study population with T2D when comparing semaglutide with non-GLP-1RA anti-diabetes medications for incident CUD (HR: 0.40, 95% CI: 0.29–0.56) and recurrent CUD (HR: 0.66, 95% CI: 0.42–1.03). While these findings provide preliminary evidence of the potential benefit of semaglutide in CUD in real-world populations, further preclinical studies are warranted to understand the underlying mechanism and randomized clinical trials are needed to support its use clinically for CUD.

Molecular Psychiatry; https://doi.org/10.1038/s41380-024-02498-5

Semaglutide and CUD: 4 emulation target trials

Trial #1 (incident CUD):

- **83,189 patients** with *obesity* and ***no prior CUD***
- **Treatment strategy:** Semaglutide (Wegovy) vs. other weight loss drugs
- **Cohort matching:** propensity-score matching for baseline characteristics
- **Outcome:** first-time CUD diagnosis
- **Follow-up:** 12-month

Trial #2 (incident CUD):

- **587,849 patients** with type 2 diabetes and ***no prior CUD***
- **Treatment strategies:** Semaglutide (Ozempic) *vs.* other anti-diabetes drugs
- **Cohort matching**: propensity-score matching for baseline characteristics
- **Outcome:** first-time CUD diagnosis
- **Follow-up**: 12-month

Trial #3 (recurrent CUD):

- **2,034** patients with obesity and ***pre-existing CUD***
- **Treatment strategy:** Semaglutide (Wegovy) vs. other weight loss drugs
- **Cohort matching:** propensity-score matching for baseline characteristics
- **Outcome**: subsequent medical encounter for CUD diagnosis
- **Follow-up:** 12-month

Trial #4 (recurrent CUD):

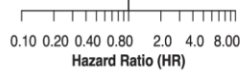
- **8,196 patients** with type 2 diabetes and ***pre-existing CUD***
- **Treatment strategies:** Semaglutide (Ozempic) *vs.* other anti-diabetes drugs
- **Cohort matching**: propensity-score matching for baseline characteristics
- **Outcome:** subsequent medical encounter for CUD diagnosis
- **Follow-up**: 12-month

Semaglutide (Wegovy) and reduced incident and recurrent CUD in patients with obesity

Incident CUD diagnosis: 44% reduction

Incident CUD diagnosis in patients with obesity and no prior history of CUD
comparison between propensity–score matched cohorts during 12–month follow–up time period

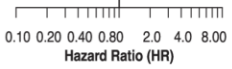
Population	Semaglutide cohort	Non–GLP–1RAs anti–obesity medications cohort	HR (95% CI)
Overall (n = 26,784/cohort)	0.28% (74)	0.48% (128)	0.56 (0.42–0.75)
Women (n = 17,938/cohort)	0.24% (43)	0.35% (63)	0.66 (0.45–0.98)
Men (n = 7,260/cohort)	0.29% (21)	0.65% (47)	0.43 (0.27–0.72)
age <= 55 years (n = 15,791/cohort)	0.32% (51)	0.52% (82)	0.61 (0.43–0.86)
age > 55 years (n = 10,639/cohort)	0.16% (17)	0.33% (35)	0.46 (0.26–0.82)
Black (n = 4,221/cohort)	0.50% (21)	0.45% (19)	1.06 (0.57–1.98)
White (n = 17,956/cohort)	0.21% (37)	0.49% (88)	0.41 (0.28–0.60)
No T2D (n = 17,754/cohort)	0.23% (40)	0.36% (63)	0.63 (0.42–0.93)
T2D (n = 8,817/cohort)	0.41% (36)	0.66% (58)	0.58 (0.38–0.88)



Recurrent CUD diagnosis: 38% reduction

Medical encounter for CUD diagnosis in patients with obesity and a prior history of CUD
comparison between propensity–score matched cohorts during 12–month follow–up time period

Population	Semaglutide cohort	Non–GLP–1RAs anti–obesity medications cohort	HR (95% CI)
Overall (n = 504/cohort)	13.0% (70)	20.4% (103)	0.62 (0.46–0.84)
Women (n = 284/cohort)	11.6% (33)	21.5% (61)	0.50 (0.33–0.76)
Men (n = 166/cohort)	13.9% (23)	26.5% (44)	0.45 (0.27–0.74)
age <= 55 years (n = 367/cohort)	14.99% (55)	22.89% (84)	0.61 (0.43–0.85)
age > 55 years (n = 97/cohort)	<10.3% (<10)	18.6% (18)	0.33 (0.14–0.80)
Black (n = 101/cohort)	11.9% (12)	17.8% (18)	0.61 (0.29–1.26)
White (n = 252/cohort)	10.3% (26)	21.8% (55)	0.45 (0.28–0.72)
No T2D (n = 209/cohort)	12.0% (25)	23.0% (48)	0.48 (0.30–0.78)
T2D (n = 255/cohort)	15.3% (39)	22.0% (56)	0.63 (0.42–0.94)



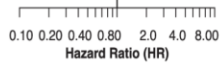
Semaglutide (Wegovy) and reduced incident and recurrent CUD in patients with type 2 diabetes

Incident CUD diagnosis: 60% reduction

Recurrent CUD diagnosis: 34% reduction

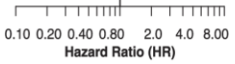
Incident CUD diagnosis in patients with type 2 diabetes and no prior history of CUD
comparison between propensity–score matched cohorts during 12–month follow–up time period

Population	Semaglutide cohort	Non–GLP–1RAs anti–diabetes medications cohort	HR (95% CI)
Overall (n = 25,820/cohort)	0.21% (54)	0.48% (123)	0.40 (0.29–0.56)
Women (n = 17,776/cohort)	0.21% (25)	0.34% (40)	0.58 (0.35–0.95)
Men (n = 12,174/cohort)	0.22% (27)	0.46% (56)	0.44 (0.28–0.69)
age <= 55 years (n = 9,997/cohort)	0.36% (36)	0.54% (54)	0.61 (0.40–0.93)
age > 55 years (n = 16,089/cohort)	0.12% (20)	0.33% (53)	0.35 (0.21–0.58)
Black (n = 3,842/cohort)	0.34% (13)	0.60% (23)	0.52 (0.27–1.03)
White (n = 15,712/cohort)	0.22% (34)	0.33% (52)	0.60 (0.39–0.93)
No obesity (n = 10,195/cohort)	0.19% (19)	0.35% (36)	0.47 (0.27–0.82)
Obesity (n = 15,609/cohort)	0.22% (34)	0.44% (69)	0.46 (0.31–0.69)



Medical encounter for CUD diagnosis in patients with type 2 diabetes and a prior history of CUD
comparison between propensity–score matched cohorts during 12–month follow–up time period

Population	Semaglutide cohort	Non–GLP–1RAs anti–diabetes medications cohort	HR (95% CI)
Overall (n = 241/cohort)	13.7% (33)	19.1% (46)	0.66 (0.42–1.03)
Women (n = 87/cohort)	12.6% (11)	21.8% (19)	0.48 (0.23–1.02)
Men (n = 125/cohort)	11.2% (14)	25.6% (32)	0.37 (0.20–0.69)
age <= 55 years (n = 128/cohort)	13.3% (17)	21.9% (28)	0.53 (0.29–0.98)
age > 55 years (n = 106/cohort)	10.4% (11)	21.7% (23)	0.40 (0.20–0.82)
Black (n = 68/cohort)	<14.7% (<10)	23.5% (16)	0.48 (0.21–1.09)
White (n = 106/cohort)	10.4% (11)	21.7% (23)	0.38 (0.18–0.77)
No obesity (n = 47/cohort)	<21.3% (<10)	<21.3% (<10)	0.55 (0.21–1.44)
Obesity (n = 190/cohort)	13.7% (26)	23.2% (44)	0.52 (0.32–0.84)



Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R*. Association of semaglutide with reduced incidence and relapse of cannabis use disorder in real-world populations: a retrospective cohort study. Molecular Psychiatry. 2024.*

Semaglutide and tobacco use disorder (TUD)

Annals of Internal Medicine ORIGINAL RESEARCH

Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes

Target Trial Emulation Using Real-World Data

William Wang; Nora D. Volkow, MD; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; and Rong Xu, PhD

Background: Reports of reduced desire to smoke in patients treated with semaglutide, a glucagon-like peptide receptor agonist (GLP-1RA) medication for type 2 diabetes mellitus (T2DM) and obesity, have raised interest about its potential benefit for tobacco use disorders (TUDs).

Objective: To examine the association of semaglutide with TUD-related health care measures in patients with comorbid T2DM and TUD.

Design: Emulation target trial based on a nationwide population-based database of patient electronic health records.

Setting: United States, 1 December 2017 to 31 March 2023.

Participants: Seven target trials were emulated among eligible patients with comorbid T2DM and TUD by comparing the new use of semaglutide versus 7 other antidiabetes medications (insulins, metformin, dipeptidyl-peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, thiazolidinediones, and other GLP-1RAs).

Measurements: The TUD-related health care measures (medical encounter for diagnosis of TUD, smoking cessation medication prescriptions, and smoking cessation counseling) that occurred within a 12-month follow-up were examined using Cox proportional hazards and Kaplan–Meier survival analyses.

Results: The study compared 222 942 new users of antidiabetes medications including 5967 of semaglutide. Semaglutide was associated with a significantly lower risk for medical encounters for TUD diagnosis compared with other antidiabetes medications, and was strongest compared with insulins (hazard ratio [HR], 0.68 [95% CI, 0.63 to 0.74]) and weakest but statistically significant compared with other GLP-1RAs (HR, 0.88 [CI, 0.81 to 0.96]). Semaglutide was associated with reduced smoking cessation medication prescriptions and counseling. Similar findings were observed in patients with and without a diagnosis of obesity. For most of the group comparisons, the differences occurred within 30 days of prescription initiation.

Limitation: Documentation bias, residual confounding, missing data on current smoking behavior, body mass index, and medication adherence.

Conclusion: Semaglutide was associated with lower risks for TUD-related health care measures in patients with comorbid T2DM and TUD compared with other antidiabetes medications including other GLP-1Ras, primarily within 30 days of prescription. These findings suggest the need for clinical trials to evaluate semaglutide's potential for TUD treatment.

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For author, article, and disclosure information, see end of text.
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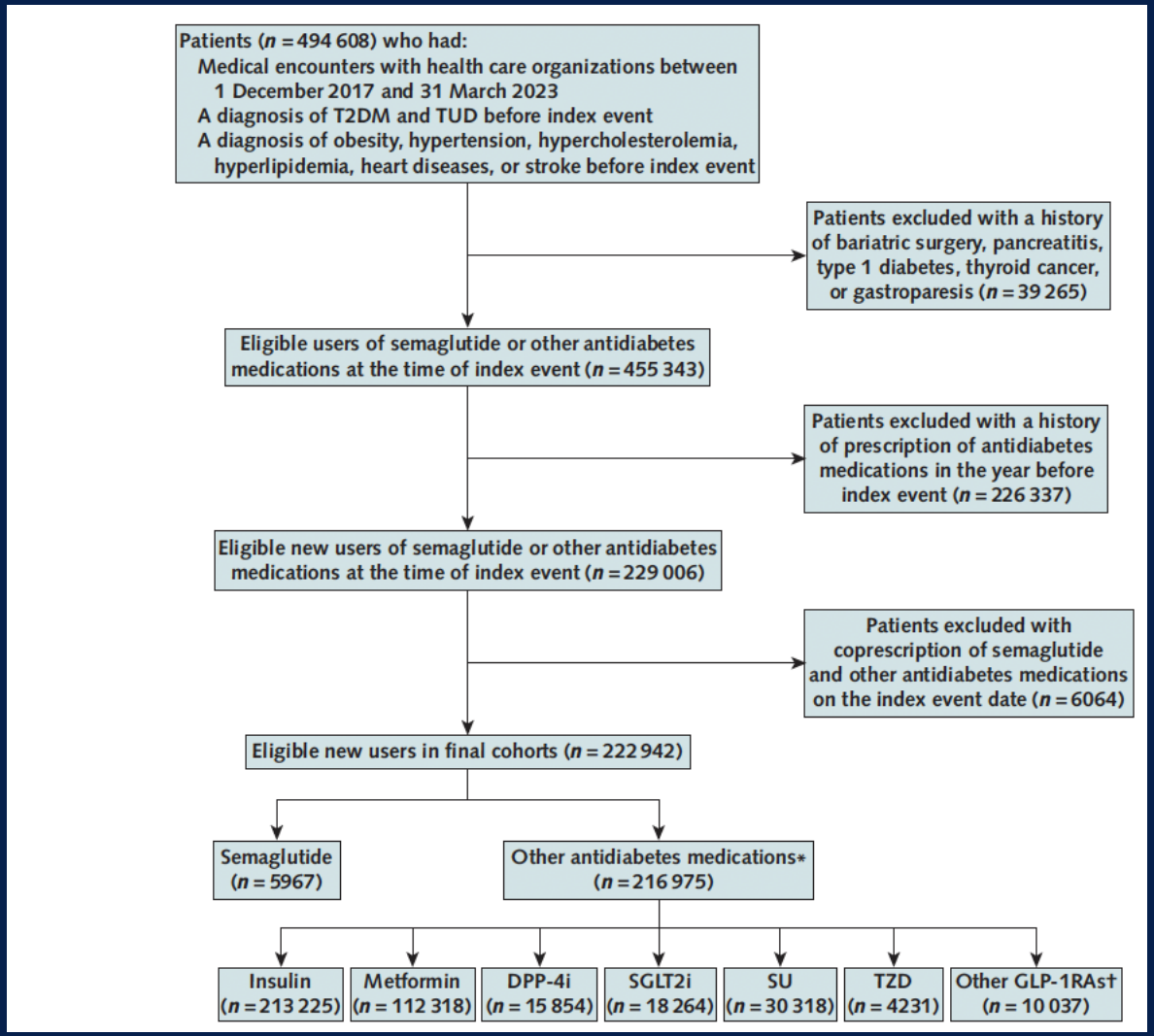
Semaglutide and TUD

222,942 Patients with T2D and pre-existing TUD

Emulation target trials:

- **222,942** patients with *type 2 diabetes* and pre-existing *TUD*
- **Treatment strategy:** Semaglutide vs. **each of 7** other anti-diabetic drugs including other GLP-1RAs.
- **Cohort matching:** propensity-score matching for baseline characteristics
- **Outcome**: subsequent medical encounter for TUD diagnosis, smoking cessation medication prescriptions, smoking cessation counseling
- **Follow-up:** 12-month



Semaglutide and reduced medical encounters for TUD diagnosis

12-30% reduction

A

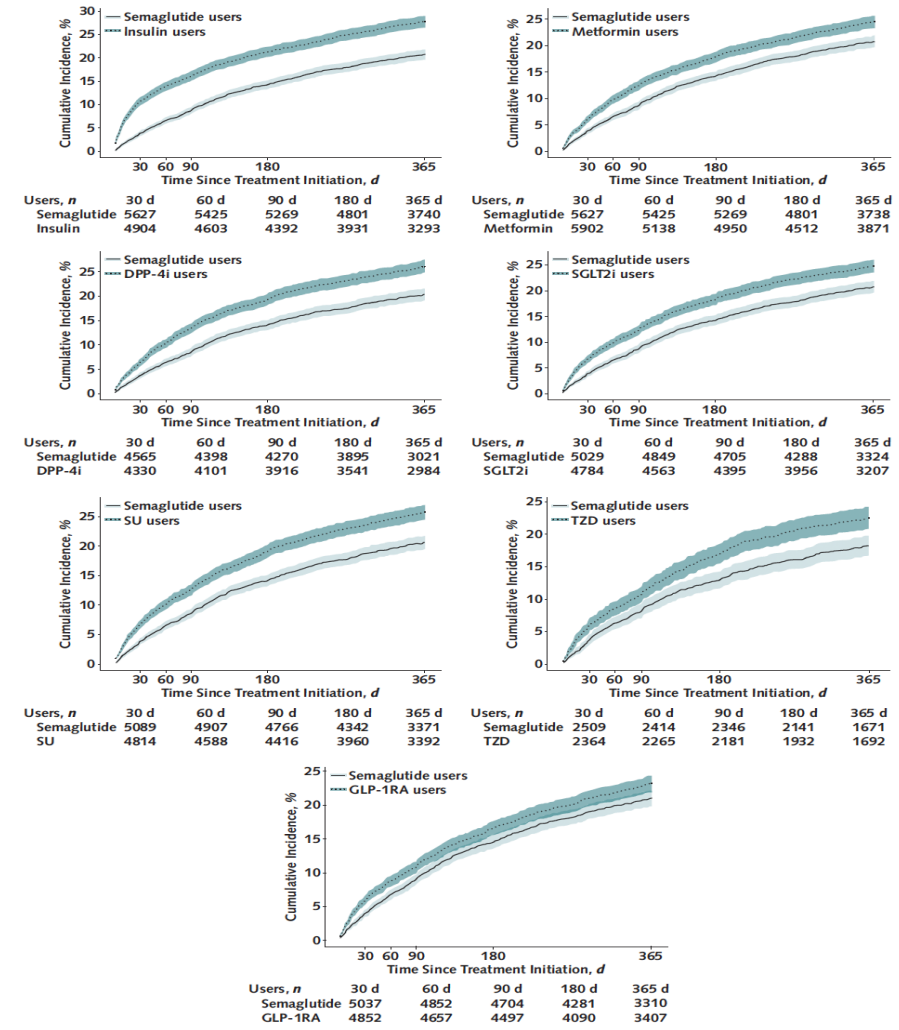
Medical encounters for TUD diagnosis in patients with T2DM and TUD
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
5,954	semaglutide	insulins	1,168 (19.6%)	1,479 (24.8%)	−5.2% (−6.7%, −3.7%)	0.68 (0.63–0.74)
5,955	semaglutide	metformin	1,170 (19.6%)	1,372 (23.0%)	−3.4% (−4.9%, −1.9%)	0.82 (0.76–0.88)
4,831	semaglutide	DPP–4i	923 (19.1%)	1,174 (24.3%)	−5.2% (−6.8%, −3.6%)	0.74 (0.67–0.80)
5,325	semaglutide	SGLT2i	1,046 (19.6%)	1,232 (23.1%)	−3.5% (−5.0%, −1.9%)	0.80 (0.74–0.87)
5,388	semaglutide	SU	1,042 (19.3%)	1,283 (23.8%)	−4.5% (−6.0%, −2.9%)	0.76 (0.70–0.83)
2,659	semaglutide	TZD	462 (17.4%)	551 (20.7%)	−3.3% (−5.5%, −1.2%)	0.78 (0.69–0.89)
5,337	semaglutide	other GLP–1RAs	1,051 (19.7%)	1,149 (21.5%)	−1.9% (−3.4%, −0.3%)	0.88 (0.81–0.96)

B

Medical encounters for TUD diagnosis in patients with T2DM and TUD (without obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
1,302	semaglutide	insulins	238 (18.3%)	326 (25.0%)	−6.8% (−9.9%, −3.6%)	0.60 (0.51–0.71)
1,305	semaglutide	metformin	240 (18.4%)	295 (22.6%)	−4.2% (−7.3%, −1.1%)	0.76 (0.64–0.90)
1,283	semaglutide	DPP–4i	237 (18.5%)	289 (22.5%)	−4.1% (−7.2%, −0.9%)	0.77 (0.65–0.92)
1,293	semaglutide	SGLT2i	238 (18.4%)	310 (24.0%)	−5.6% (−8.7%, −2.4%)	0.70 (0.59–0.83)
1,292	semaglutide	SU	237 (18.3%)	297 (23.0%)	−4.6% (−7.8%, −1.5%)	0.74 (0.62–0.88)
1,033	semaglutide	TZD	188 (18.2%)	223 (21.6%)	−3.4% (−6.8%, 0.1%)	0.78 (0.64–0.94)
1,268	semaglutide	other GLP–1RAs	232 (18.3%)	256 (20.2%)	−1.9% (−5.0%, 1.2%)	0.85 (0.71–1.02)

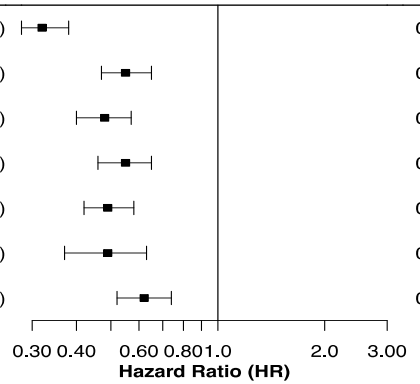


Semaglutide and reduced smoking cessation medication prescriptions

A

Smoking cessation medication prescriptions in patients with T2DM and TUD
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

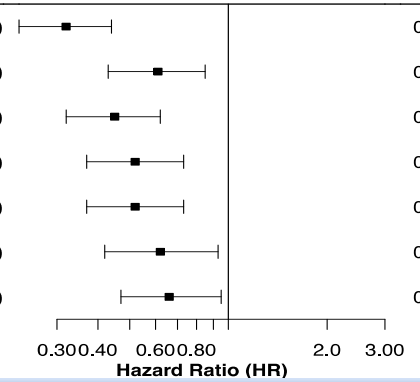
Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
5,954	semaglutide	insulins	242 (4.1%)	670 (11.3%)	–7.2% (–8.1%, –6.2%)	0.32 (0.28–0.38)
5,955	semaglutide	metformin	244 (4.1%)	428 (7.2%)	–3.1% (–3.9%, –2.3%)	0.55 (0.47–0.65)
4,831	semaglutide	DPP–4i	187 (3.9%)	372 (7.7%)	–3.8% (–4.8%, –2.9%)	0.48 (0.40–0.57)
5,325	semaglutide	SGLT2i	211 (4.0%)	369 (6.9%)	–3.0% (–3.8%, –2.1%)	0.55 (0.46–0.65)
5,388	semaglutide	SU	215 (4.0%)	418 (7.8%)	–3.8% (–4.7%, –2.9%)	0.49 (0.42–0.58)
2,659	semaglutide	TZD	81 (3.0%)	159 (6.0%)	–2.9% (–4.0%, –1.8%)	0.49 (0.37–0.63)
5,337	semaglutide	other GLP–1RAs	212 (4.0%)	331 (6.2%)	–2.2% (–3.1%, –1.4%)	0.62 (0.52–0.74)



B

Smoking cessation medication prescriptions in patients with T2DM and TUD (without obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
1,302	semaglutide	insulins	54 (4.1%)	148 (11.4%)	–7.2% (–9.3%, –5.2%)	0.32 (0.23–0.44)
1,305	semaglutide	metformin	54 (4.1%)	85 (6.5%)	–2.4% (–4.1%, –0.7%)	0.61 (0.43–0.85)
1,283	semaglutide	DPP–4i	51 (4.0%)	109 (8.5%)	–4.5% (–6.4%, –2.7%)	0.45 (0.32–0.62)
1,293	semaglutide	SGLT2i	54 (4.2%)	98 (7.6%)	–3.4% (–5.2%, –1.6%)	0.52 (0.37–0.73)
1,292	semaglutide	SU	52 (4.0%)	95 (7.4%)	–3.3% (–5.1%, –1.5%)	0.52 (0.37–0.73)
1,033	semaglutide	TZD	41 (4.0%)	62 (6.0%)	–2.0% (–3.0%, –0.2%)	0.62 (0.42–0.93)
1,268	semaglutide	other GLP–1RAs	52 (4.1%)	75 (5.9%)	–1.8% (–3.5%, –0.1%)	0.66 (0.47–0.95)



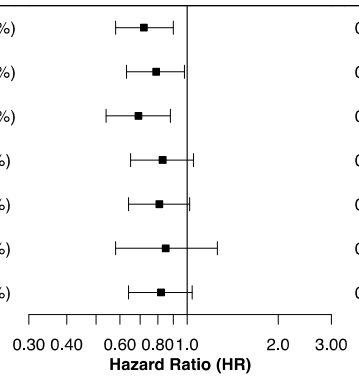
40-70% reduction

Semaglutide and reduced smoking cessation counseling

A

Smoking cessation counseling in patients with T2DM and TUD
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

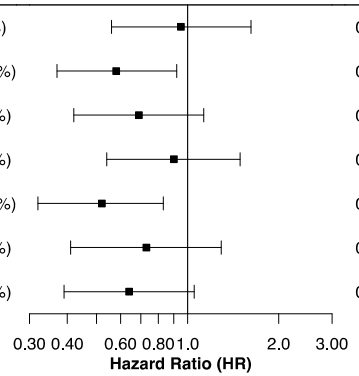
Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
5,954	semaglutide	insulins	140 (2.4%)	178 (3.0%)	–0.6% (–1.2%, –0.1%)	0.72 (0.58–0.90)
5,955	semaglutide	metformin	140 (2.4%)	176 (3.0%)	–0.6% (–1.2%, –0.0%)	0.79 (0.63–0.98)
4,831	semaglutide	DPP–4i	109 (2.3%)	154 (3.2%)	–0.9% (–1.6%, –0.3%)	0.69 (0.54–0.88)
5,325	semaglutide	SGLT2i	122 (2.3%)	143 (2.7%)	–0.4% (–1.0%, 0.2%)	0.83 (0.65–1.05)
5,388	semaglutide	SU	127 (2.4%)	153 (2.8%)	–0.5% (–1.1%, 0.1%)	0.81 (0.64–1.02)
2,659	semaglutide	TZD	47 (1.8%)	53 (2.0%)	–0.2% (–1.0%, 0.5%)	0.85 (0.58–1.26)
5,337	semaglutide	other GLP–1RAs	124 (2.3%)	149 (2.8%)	–0.5% (–1.1%, 0.1%)	0.82 (0.64–1.04)



B

Smoking cessation counseling in patients with T2DM and TUD (without obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
1,302	semaglutide	insulins	28 (2.1%)	26 (2.0%)	0.2% (–0.9%, 1.2%)	0.95 (0.56–1.62)
1,305	semaglutide	metformin	29 (2.2%)	48 (3.7%)	–1.5% (–2.8%, –0.2%)	0.58 (0.37–0.82)
1,283	semaglutide	DPP–4i	27 (2.1%)	38 (3.0%)	–0.9% (–2.1%, 0.4%)	0.69 (0.42–1.13)
1,293	semaglutide	SGLT2i	29 (2.2%)	31 (2.4%)	–0.2% (–1.3%, 1.0%)	0.90 (0.54–1.49)
1,292	semaglutide	SU	27 (2.1%)	50 (3.9%)	–1.8% (–3.1%, –0.5%)	0.52 (0.32–0.83)
1,033	semaglutide	TZD	21 (2.0%)	27 (2.6%)	–0.6% (–1.9%, 0.7%)	0.73 (0.41–1.29)
1,268	semaglutide	other GLP–1RAs	26 (2.1%)	39 (3.1%)	–1.0% (–2.3%, 0.2%)	0.64 (0.39–1.05)



20-30% reduction

Wang W, Volkow ND, Berger NA, Davis PB, Kaelber DC, Xu R*. Association of semaglutide with tobacco use disorder in patients with type 2 diabetes: target trial emulation using real-world data. Annals of Internal Medicine 2024*

Semaglutide and opioid overdose

JAMA Network Open

Research Letter | Psychiatry

Semaglutide and Opioid Overdose Risk in Patients With Type 2 Diabetes and Opioid Use Disorder

William Wang; Nora D. Volkow, MD; QuangQiu Wang, MS; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; Rong Xu, PhD

Introduction

Drug overdose fatalities in the United States remain high, with an estimated 107 543 deaths in 2023, mostly from opioids.[1] Despite the effectiveness of medications for opioid use disorder (OUD) in preventing overdoses, only an estimated 25% of individuals with OUD receive them,[2] and close to 50% discontinue treatment within 6 months. There is an urgency for alternative treatments for OUD. Glucagon-like peptide-1 receptor agonists (GLP1-RAs), used for type 2 diabetes (T2D) and obesity, modulated dopamine reward signaling and decreased drug rewards, including heroin in rodents.[3] Anecdotal reports of reduced drug craving in individuals using semaglutide, a new generation GLP-1RA, along with empirical studies showed its therapeutic benefits in alcohol and nicotine use disorders.[4,5] This led us to investigate whether semaglutide could protect against overdoses in patients with OUD.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Semaglutide and opioid overdose

33,006 Patients with T2D and pre-existing opioid use disorder

40-60% reduction in opioid overdose

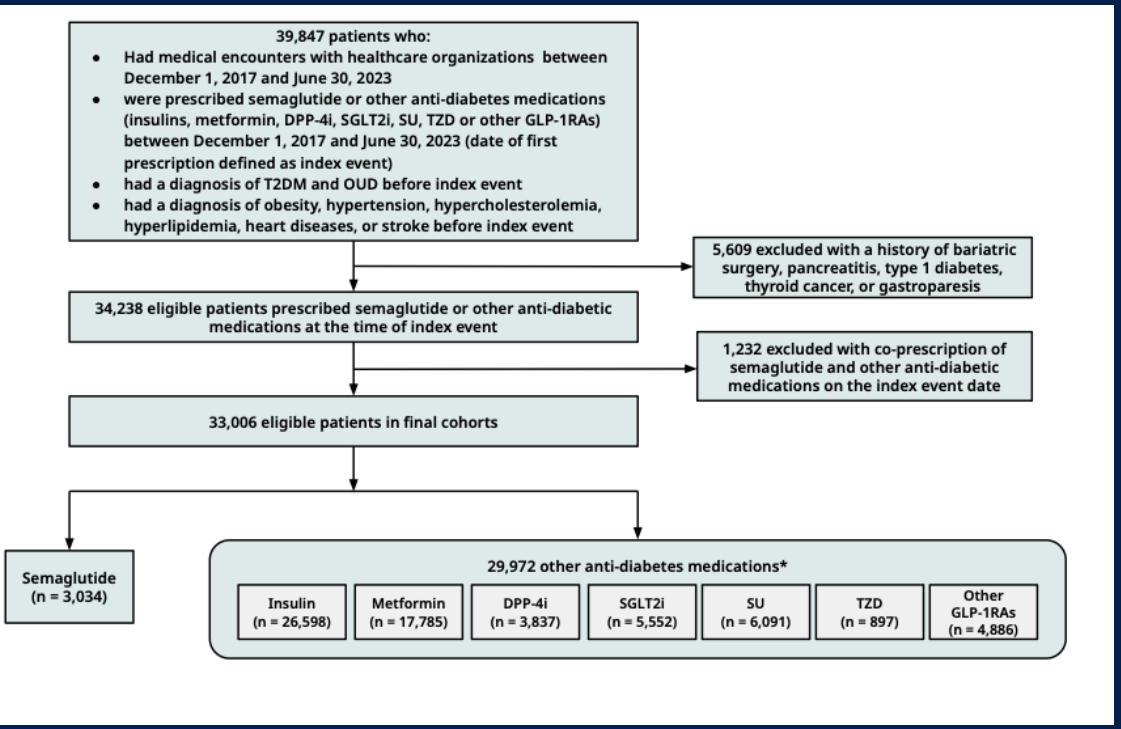
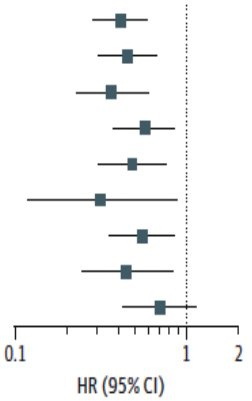
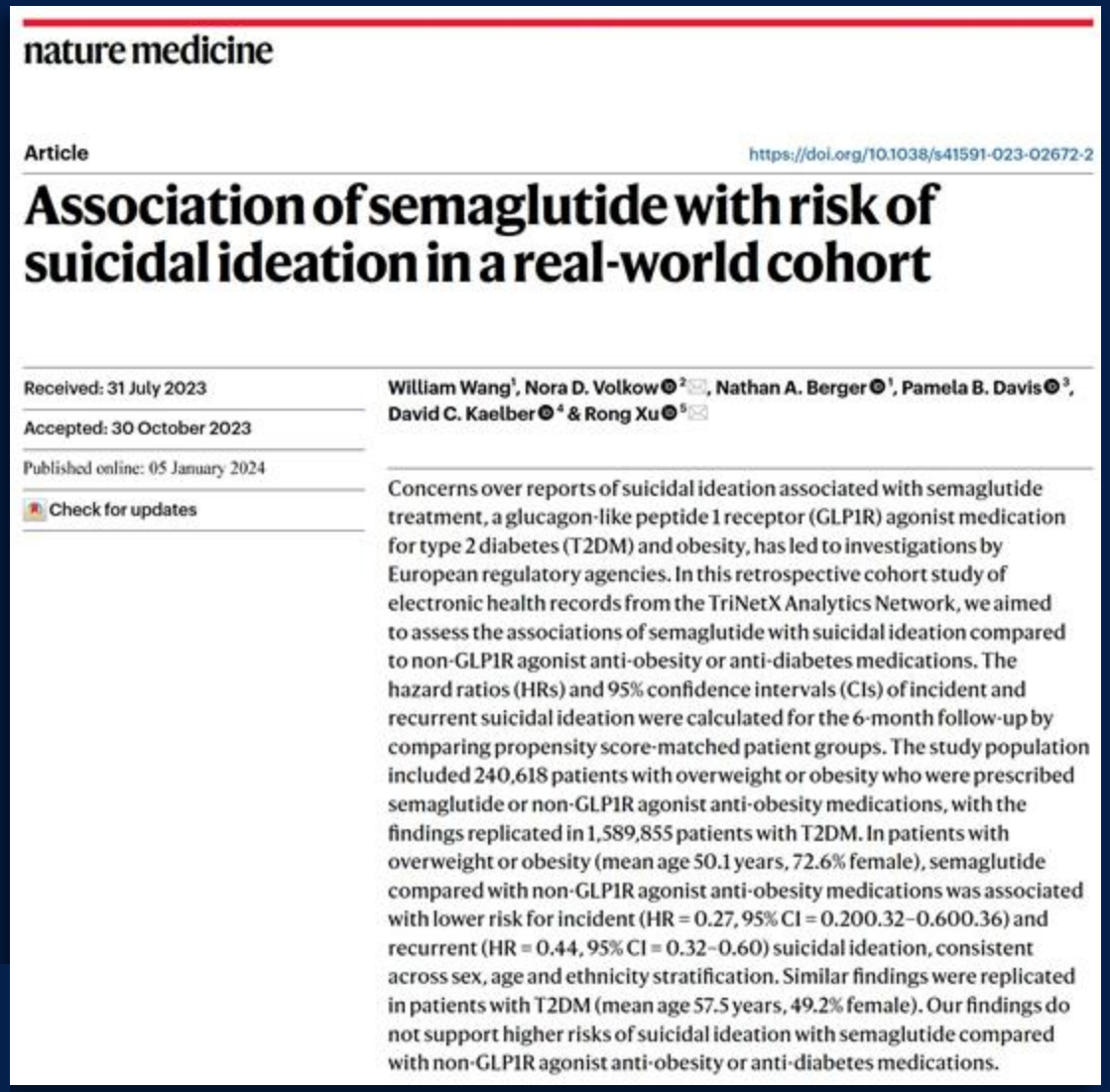


Figure. Risk of Opioid Overdose in Patients With Type 2 Diabetes and Opioid Use Disorders, Comparing Propensity-Score Matched Semaglutide With Other Antidiabetic Medication Groups

Comparison	Participants, No.	Cases in semaglutide group, No. (%)	Cases in comparison group, No. (%)	Risk difference, % (95% CI)	HR (95% CI)
Semaglutide vs insulin	2790	42 (1.51)	97 (3.48)	-1.97 (-2.79 to -1.16)	0.42 (0.29-0.60)
Semaglutide vs metformin	2605	35 (1.34)	76 (2.92)	-1.57 (-2.36 to -0.79)	0.46 (0.31-0.68)
Semaglutide vs DPP-4i	1751	22 (1.26)	57 (3.26)	-2.00 (-2.98 to -1.02)	0.37 (0.23-0.61)
Semaglutide vs SGLT2i	2361	36 (1.53)	61 (2.58)	-1.06 (-1.87 to -0.25)	0.58 (0.38-0.87)
Semaglutide vs sulfonylureas	2128	27 (1.27)	54 (2.54)	-1.27 (-2.09 to -0.45)	0.49 (0.31-0.78)
Semaglutide vs thiazolidinediones	723	<10 (<1.38)	15 (2.08)	-0.69 (-2.04 to 0.65)	0.32 (0.12-0.89)
Semaglutide vs other GLP-1RAs	2406	31 (1.29)	55 (2.29)	-1.00 (-1.75 to -0.25)	0.56 (0.36-0.87)
Semaglutide vs liraglutide	1186	15 (1.27)	33 (2.78)	-1.52 (-2.65 to -0.39)	0.45 (0.25-0.84)
Semaglutide vs dulaglutide	2204	27 (1.23)	38 (1.72)	-0.50 (-1.21 to 0.21)	0.71 (0.43-1.15)



Semaglutide and suicidal ideations



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

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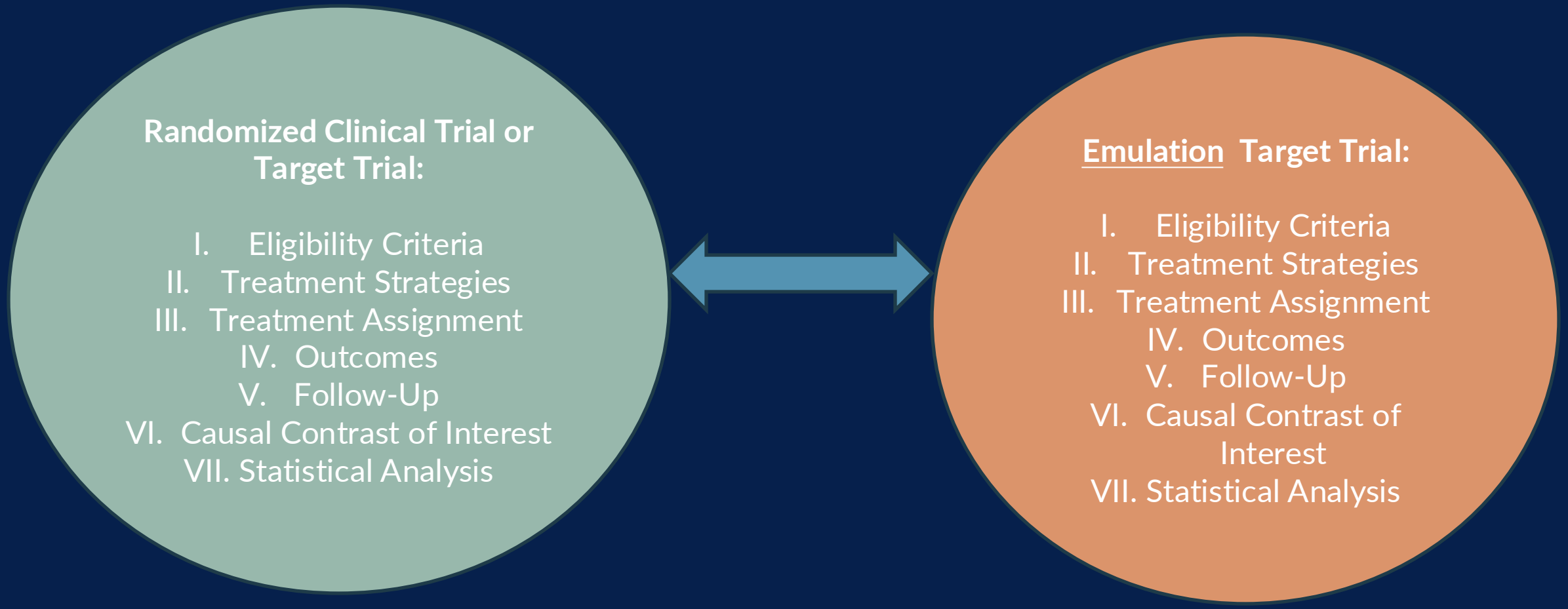
Check for updates

William Wang[1], Nora D. Volkow[2], Nathan A. Berger[1], Pamela B. Davis[3], David C. Kaelber[4] & Rong Xu[5]

Concerns over reports of suicidal ideation associated with semaglutide treatment, a glucagon-like peptide 1 receptor (GLP1R) agonist medication for type 2 diabetes (T2DM) and obesity, has led to investigations by European regulatory agencies. In this retrospective cohort study of electronic health records from the TriNetX Analytics Network, we aimed to assess the associations of semaglutide with suicidal ideation compared to non-GLP1R agonist anti-obesity or anti-diabetes medications. The hazard ratios (HRs) and 95% confidence intervals (CIs) of incident and recurrent suicidal ideation were calculated for the 6-month follow-up by comparing propensity score-matched patient groups. The study population included 240,618 patients with overweight or obesity who were prescribed semaglutide or non-GLP1R agonist anti-obesity medications, with the findings replicated in 1,589,855 patients with T2DM. In patients with overweight or obesity (mean age 50.1 years, 72.6% female), semaglutide compared with non-GLP1R agonist anti-obesity medications was associated with lower risk for incident (HR = 0.27, 95% CI = 0.200.32–0.600.36) and recurrent (HR = 0.44, 95% CI = 0.32–0.60) suicidal ideation, consistent across sex, age and ethnicity stratification. Similar findings were replicated in patients with T2DM (mean age 57.5 years, 49.2% female). Our findings do not support higher risks of suicidal ideation with semaglutide compared with non-GLP1R agonist anti-obesity or anti-diabetes medications.

- In July 2023. concerns raised by EMA and FDA about potential risk of suicidal thoughts associated with semaglutide.
- Our study showed that semaglutide was associated with a 50%–80% reduced risk. Published in Nature Medicine on January 5, 2024
- 6 days later on January 11, 2024, FDA cleared semaglutide of suicidal risk
- 3 months later in April 2024. EMA cleared semaglutide of suicidal risk

Semaglutide and substance use disorders: target trial emulation using real-world data



Trial Participants (hundreds)
Cost: $ 10-50 million

Real-World Patients (millions)
Cost: $ <1 million

Summary, limitations and future directions

Summary:

- Real-world data (RWD) supporting the potential preventive or therapeutic benefits of semaglutide on substance use disorders.

Advantages:

- Real-time, cost-effective: millions of people are taking semaglutide. Routinely collected data. Data is updated on a daily basis
- Real-world: comorbidities, comedications, demographics, socioeconomic factors.

Limitations:

- RWD: confounders and biases.
- RCT outcomes are not explicitly captured in RWD.

Future works:

- Randomized clinical trials.
- Parallel RCTs and emulation RCTs using RWD to inform each other.
- Mechanisms of action.
- Polysubstance use disorders, comorbidities

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- David C Kaelber (MetroHealth and CWRU)

QUESTIONS?

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