JAMA Psychiatry | Brief Report

# Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder

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**IMPORTANCE** Preliminary studies suggest that glucagon-like peptide-1 receptor (GLP-1) agonists, used to treat type 2 diabetes and obesity, may decrease alcohol consumption.

**OBJECTIVE** To test whether the risk of hospitalization due to alcohol use disorder (AUD) is decreased during the use of GLP-1 agonists compared with periods of nonuse for the same individual.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study was an observational study conducted nationwide in Sweden using data from January 2006 to December 2023. The population-based cohort was identified from registers of inpatient care, specialized outpatient care, sickness absence, and disability pension. Participants were all residents aged 16 to 64 years who had a diagnosis of AUD.

**EXPOSURES** The primary exposure was use of individual GLP-1 agonists (compared with nonuse of GLP-1 agonists), and the secondary exposure was medications with indication for AUD.

**MAIN OUTCOMES AND MEASURES** The primary outcome was AUD hospitalization analyzed in a Cox regression within-individual model. Secondary outcomes were any substance use disorder (SUD)–related hospitalization, somatic hospitalization, and suicide attempt.

**RESULTS** The cohort included 227 866 individuals with AUD; 144 714 (63.5%) were male and 83 154 (36.5%) were female, with a mean (SD) age of 40.0 (15.7) years. Median (IQR) follow-up time was 8.8 (4.0-13.3) years. A total of 133 210 individuals (58.5%) experienced AUD hospitalization. Semaglutide (4321 users) was associated with the lowest risk (AUD: adjusted hazard ratio [aHR], 0.64; 95% CI, 0.50-0.83; any SUD: aHR, 0.68; 95% CI, 0.54-0.85) and use of liraglutide (2509 users) with the second lowest risk (AUD: aHR, 0.72; 95% CI, 0.57-0.92; any SUD: aHR, 0.78; 95% CI, 0.64-0.97) of both AUD and SUD hospitalization. Use of any AUD medication was associated with a modestly decreased risk (aHR, 0.98; 95% CI, 0.96-1.00). Semaglutide (aHR, 0.78; 95% CI, 0.68-0.90) and liraglutide (aHR, 0.79; 95% CI, 0.69-0.91) use were also associated with decreased risk of somatic hospitalizations but not associated with suicide attempts (semaglutide: aHR, 0.55; 95% CI, 0.23-1.30; liraglutide: aHR, 1.08; 95% CI, 0.55-2.15).

**CONCLUSIONS AND RELEVANCE** Among patients with AUD and comorbid obesity/type 2 diabetes, the use of semaglutide and liraglutide were associated with a substantially decreased risk of hospitalization due to AUD. This risk was lower than that of officially approved AUD medications. Semaglutide and liraglutide may be effective in the treatment of AUD, and clinical trials are urgently needed to confirm these findings.

Supplemental content

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According to the World Health Organization, harmful use of alcohol is accountable for 5.1% of the global burden of disease.[1] Psychosocial treatments are the cornerstone of alcohol use disorder (AUD) treatment, but pharmacological treatments are also beneficial, although underused.[2,3]

Glucagon-like peptide-1 receptor (GLP-1) agonists are approved for clinical use to treat diabetes and obesity. Preclinical studies in rodents and monkeys, as well as human case reports, have shown that GLP-1 agonists can reduce alcohol consumption.[4-6] In humans, genetic variation in *GLP-1R* has been shown to be associated with increased risk of AUD.[7] A recent registry study from Denmark has also shown that use of GLP-1 agonists has been linked to transient (3-month) reduced risk of subsequent alcohol-related events.[8]

We aimed to investigate the potential of GLP-1 agonists as a treatment for reducing alcohol-related harms by analyzing real-world data from Swedish registries.

### Key Points

**Question** Are glucagon-like peptide-1 receptor (GLP-1) agonists effective in the treatment of alcohol use disorder?

**Findings** This cohort study with a median follow-up time of more than 8 years indicates that individuals are at markedly lower risk of alcohol-related hospitalizations and hospitalizations due to somatic reasons when using GLP-1 agonists, especially semaglutide, as compared with times they are not using them.

**Meaning** GLP-1 agonists, especially semaglutide, offer promise as a novel treatment to reduce alcohol consumption and to prevent development of alcohol-related outcomes, but randomized clinical trials are needed to verify these initial findings.

## Methods

### Study Design and Cohort Acquisition

Swedish nationwide electronic registries were used to obtain and combine data through personal deidentified identification numbers. The project was approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden (Dnr: 2007/762-31 and Dnr: 2021-06441-02). Informed consent is not required in Sweden for register-based studies, where no contact is made with the patient.

The National Patient registry (inpatient and specialized outpatient visits) and Microdata for Analysis of Social Insurance register (data on sickness absence and disability pension

Table. Characteristics of the Whole Cohort and Subcohorts of Patients Who Used GLP-1 Agonists and Those Who Used AUD Medications During Follow-Up[a]

| Characteristic | No. (%) | | |
|---|---|---|---|
| | All patients (N = 227 868) | GLP-1 agonist users (n = 6276) | AUD medication users (n = 75 454) |
| Age, mean (SD), y | 40.0 (15.7) | 46.0 (12.5) | 45.4 (12.4) |
| Sex | | | |
| Male | 144 714 (63.5) | 4058 (64.7) | 50 246 (66.6) |
| Female | 83 154 (36.5) | 2218 (35.3) | 25 208 (33.4) |
| Country of birth | | | |
| Sweden | 193 719 (85.0) | 5131 (81.8) | 65 893 (87.3) |
| Other European country | 20 721 (9.1) | 640 (10.2) | 6946 (9.2) |
| Outside Europe | 13 426 (5.9) | 505 (8.1) | 2615 (3.5) |
| Sickness absence during previous year before cohort entry | | | |
| 0 d | 184 070 (80.8) | 4561 (72.7) | 54 417 (72.1) |
| 1-90 d | 28 239 (12.4) | 1032 (16.4) | 13 659 (18.1) |
| >90 d | 15 557 (6.8) | 683 (10.9) | 7378 (9.8) |
| Disability pension | 32 818 (14.4) | 1162 (18.5) | 11 437 (15.2) |
| Type of AUD diagnosis at baseline[b] | | | |
| Acute intoxication (F10.0) | 90 225 (39.6) | 1951 (31.1) | 10 973 (14.5) |
| Dependence syndrome (F10.2) | 63 849 (28.0) | 2131 (34.0) | 34 160 (45.3) |
| Harmful use (F10.1) | 49 100 (21.6) | 1539 (24.5) | 20 435 (27.1) |
| Other/unspecified | 203 174 (10.8) | 655 (10.4) | 9886 (13.1) |
| Other substance use disorder before baseline | 8899 (3.9) | 285 (4.5) | 3198 (4.2) |
| Suicide attempt before baseline | 20 349 (8.9) | 794 (12.7) | 7460 (9.9) |
| Diseases recorded by end of follow-up | | | |
| Type 2 diabetes | 14 787 (6.5) | 2745 (43.7) | 5999 (8.0) |
| Cardiovascular disease | 60 251 (26.4) | 3178 (50.6) | 25 176 (33.4) |
| Kidney disease | 13 634 (6.0) | 671 (10.7) | 5094 (6.8) |
| Obesity | 10 818 (4.8) | 1175 (18.7) | 4998 (6.6) |

Abbreviations: AUD, alcohol use disorder; GLP-1, glucagon-like peptide-1 receptor.

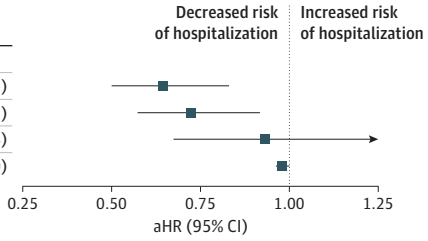
[a] Before cohort entry/before baseline data recorded from 1997 onwards. Sociodemographic variables were derived from the longitudinal integrated database for health insurance and labor market studies register.

[b] Parentheses include codes from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*.

Figure 1. Risk of Hospitalization Due to Alcohol Use Disorder (AUD) and Substance Use Disorder (SUD)

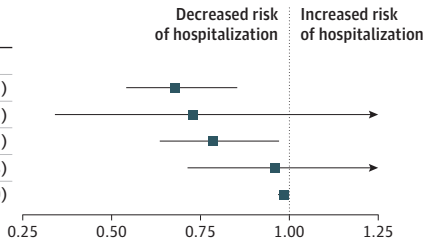
A Risk of hospitalization due to AUD associated with use of GLP-1 agonists and AUD medications in within-individual model of persons with AUD

| Drug | No. Users | Events | PYs | aHR (95% CI) |
|---|---|---|---|---|
| GLP-1 agonists | | | | |
| Semaglutide | 4321 | 222 | 4677 | 0.64 (0.50-0.83) |
| Liraglutide | 2509 | 212 | 3076 | 0.72 (0.57-0.92) |
| Dulaglutide | 1118 | 139 | 1443 | 0.93 (0.68-1.28) |
| AUD medications | 75454 | 30198 | 73222 | 0.98 (0.96-1.00) |




B Risk of hospitalization due to substance use disorder associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

| Drug | No. Users | Events | PYs | aHR (95% CI) |
|---|---|---|---|---|
| GLP-1 agonists | | | | |
| Semaglutide | 4321 | 281 | 4667 | 0.68 (0.54-0.85) |
| Exenatide | 98 | 13 | 167 | 0.73 (0.34-1.55) |
| Liraglutide | 2509 | 262 | 3076 | 0.78 (0.64-0.97) |
| Dulaglutide | 1118 | 172 | 1443 | 0.96 (0.71-1.28) |
| AUD medications | 75454 | 32543 | 73222 | 0.98 (0.97-1.00) |




The use of individual glucagon-like peptide-1 receptor (GLP-1) agonists was compared with nonuse of GLP-1 agonists. Groupwise and use of specific AUD medications were compared with nonuse of AUD medications. Both of these models (A and B) were adjusted for time-varying use of psychotropic medications (antipsychotics, N05A; antidepressants, N06A; mood stabilizers, including carbamazepine, N03AF01; valproic acid, N03AG01; lamotrigine, N03AX09; and lithium, N05AN01), benzodiazepines and related drugs (N05BA, N05CD, N05CF), and attention-deficit/hyperactivity disorder (ADHD) medications (N06BA); use of antidiabetic drugs other than GLP-1 agonists (A10 excluding A10BJ); temporal order of GLP-1 medication; and time since cohort entry. aHR indicates adjusted hazard ratio.

diagnoses) were used to identify individuals diagnosed with AUD (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*], code F10) during the years 2006-2021 who were age 16 to 65 years. This produced a cohort of 227 886 individuals who were followed up from AUD diagnosis to death, emigration, or end of data linkage (December 31, 2023), whichever came first.

## Exposure

Individual drug use periods were constructed using the PRE2DUP method with data from the National Prescribed Drug Register.[9,10] The main exposure was GLP-1 agonists, which were exenatide, liraglutide, dulaglutide, and semaglutide; lixisenatide was excluded because of sparsity of use. The secondary exposure was use of AUD medications (disulfiram, acamprosate, and naltrexone; nalmefene excluded because of sparsity of use). A group category including all the previously mentioned AUD medications was also constructed.

## Outcomes

The main outcome measure was hospitalization due to AUD (*ICD-10* F10). Secondary outcomes were hospitalization due to substance use disorder (SUD) (F10-F16, F18-F19), hospitalization due to somatic reasons (A00-N99, U07[ = COVID-19], but excluding F00-F99), and hospitalization due to suicide attempt (X60-X84, Y10-Y34).

## Statistical Analysis

We used a within-individual design where each individual acts as their own control. Cox regression models with fixed effects were used to calculate the within-individual risk of an outcome associated with use vs nonuse of pharmacotherapies (eFigures 1 and 2 in Supplement 1).[11] The use of individual GLP-1 agonists was compared with nonuse of GLP-1 agonists. Groupwise and use of specific AUD medications were compared with nonuse of AUD medications.

Results are presented as adjusted hazard ratios (aHRs) and 95% CIs. Exposures with fewer than 10 events were excluded from the figures (exenatide for AUD and suicide attempt analyses). Data analyses were conducted from April to September 2024 and used SAS version 9.4 (SAS Institute).

# Results

The total cohort consisted of 227 868 individuals with an AUD, of whom 144 714 (63.5%) were male and 83 154 (36.5%) female (**Table**). Their mean (SD) age was 40.0 (15.7) years at cohort entry, and 193 719 (85%) were born in Sweden. The cohort included 6276 individuals with both an AUD and use of GLP-1 agonists. Of this subcohort, 4058 (64.7%) were male and 2218 (35.3) female; the mean (SD) age for the subcohort was 46.0 (12.5) years. The cohort was followed up for a median (IQR) of 8.8 (4.0-13.3) years.

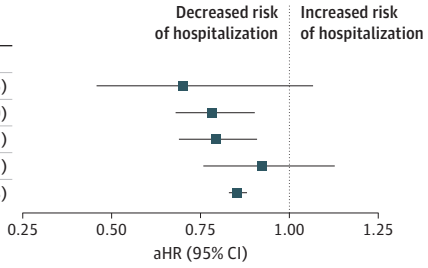
## Risk of Hospitalization Due to AUD and SUD

A total of 133 210 individuals were hospitalized because of AUD and 138 390 because of any SUD at least once. Use of semaglutide was associated with the lowest risk (AUD: aHR, 0.64; 95% CI, 0.50-0.83; any SUD: aHR, 0.68, 95% CI, 0.54-0.85) and use of liraglutide with the second lowest risk (AUD: aHR, 0.72; 95% CI, 0.57-0.92; any SUD: aHR, 0.78; 95% CI, 0.64-0.97) of both AUD and SUD hospitalization (**Figure 1**). Use of AUD medications in general was not associated with significantly altered risk of either AUD or SUD hospitalization (AUD: aHR, 0.98; 95% CI, 0.96-1.00; any SUD: aHR, 0.98; 95% CI, 0.97-1.00), al-

Figure 2. Risk of Hospitalization Due to Somatic Reasons and Suicide Attempt

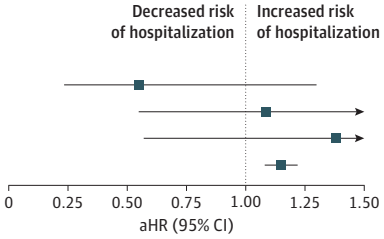
A Risk of somatic hospitalization associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

| Drug | No. Users | Events | PYs | aHR (95% CI) |
|---|---|---|---|---|
| GLP-1 agonists | | | | |
| Exenatide | 98 | 50 | 167 | 0.70 (0.46-1.06) |
| Semaglutide | 4321 | 708 | 4677 | 0.78 (0.68-0.90) |
| Liraglutide | 2509 | 613 | 3076 | 0.79 (0.69-0.91) |
| Dulaglutide | 1118 | 362 | 1443 | 0.92 (0.76-1.12) |
| AUD medications | 75454 | 9995 | 73222 | 0.85 (0.83-0.88) |




B Risk of suicide attempt associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

| Drug | No. Users | Events | PYs | aHR (95% CI) |
|---|---|---|---|---|
| GLP-1 agonists | | | | |
| Semaglutide | 4321 | 32 | 4677 | 0.55 (0.23-1.30) |
| Liraglutide | 2509 | 28 | 3076 | 1.08 (0.55-2.15) |
| Dulaglutide | 1118 | 19 | 1443 | 1.38 (0.57-3.34) |
| AUD medications | 75454 | 3265 | 73222 | 1.15 (1.08-1.22) |




The use of individual glucagon-like peptide-1 receptor (GLP-1) agonists was compared with nonuse of GLP-1 agonists. Groupwise and use of specific alcohol use disorder (AUD) medications were compared with nonuse of AUD medications. Both of these models (A and B) were adjusted for time-varying use of psychotropic medications (antipsychotics, N05A; antidepressants, N06A; mood stabilizers, including carbamazepine, N03AF01; valproic acid, N03AG01; lamotrigine, N03AX09; and lithium, N05AN01), benzodiazepines and related drugs (N05BA, N05CD, N05CF), and attention-deficit/hyperactivity disorder medications (N06BA); use of antidiabetic drugs other than GLP-1 agonists (A10 excluding A10BJ); temporal order of GLP-1 medication; and time since cohort entry. aHR indicates adjusted hazard ratio.

though use of naltrexone was associated with reduced risk (AUD: aHR, 0.86; 95% CI, 0.83-0.89; any SUD: aHR, 0.86; 95% CI, 0.84-0.90). The results for individual AUD medications are shown in eTable 1 in Supplement 1. Additional sensitivity analyses to assess bias are presented in eTables 2 and 3 in Supplement 1.

### Risk of Hospitalization Due to Somatic Reasons and Suicide Attempts

A total of 83 166 individuals were hospitalized for somatic reasons and 22 231 for suicide attempt. Use of semaglutide was associated with the lowest risk (aHR, 0.78; 95% CI, 0.68-0.90) and use of liraglutide with the second lowest risk (aHR, 0.79; 95% CI, 0.69-0.91) of somatic hospitalization (**Figure 2**). Use of AUD medications in general was associated with reduced risk of somatic hospitalization (aHR, 0.85; 95% CI, 0.83-0.88).

Use of GLP-1 agonists was not associated with a statistically significantly altered risk of suicide attempt (semaglutide: aHR, 0.55, 95% CI, 0.23-1.30). However, use of AUD medications in general was associated with an increased risk of suicide attempt (aHR, 1.15, 95% CI, 1.08-1.22). The results for individual AUD medications are shown in eTable 1 in Supplement 1.

## Discussion

In this nationwide register-based study, the GLP-1 agonists semaglutide and liraglutide, but not other GLP-1 agonists, were associated with a markedly reduced risk of AUD- and SUD-related hospitalizations as well as somatic hospitalizations. We did not observe statistically significant changes in risk of suicide attempts for GLP-1 agonists, although the point estimate of 0.55 for semaglutide suggests it may be associated with decreased risk of suicide. Especially interesting is the notion that semaglutide and liraglutide were associated with better outcomes than AUD medications (naltrexone, disulfiram, and acamprosate), although this comparison needs to be taken with a grain of salt, as the comparators were different: GLP-1 agonist use was compared with the times GLP-1 agonists were not used, and AUD medication use compared with times when AUD medications were not used.

The result for SUD-related hospitalizations needs to be interpreted cautiously, as the majority of these hospitalizations were from alcohol-related causes. However, this result is in line with a recent registry study, which found that use of semaglutide was associated with reduced incidence and relapse of cannabis use disorder.[12] As the GLP-1 receptor has been shown to be involved in many pathways related to craving and reward,[13] it may be plausible that GLP-1 agonists could be used for a wide variety of addictions. A recent review suggested that GLP-1 agonists may exert a centrally mediated effect to reduce addictive behavior at least partly via dopamine modulation.[14]

### Limitations

Because this is an observational study, it can only speak for associations, not causality. Further strengths and weaknesses are discussed in the eAppendix in Supplement 1.

## Conclusions

AUDs and SUDs are undertreated pharmacologically, despite the availability of effective treatments. However, novel treatments are also needed because existing treatments may not be suit-

able for all patients. GLP-1 agonists, and especially semaglutide and liraglutide, may be effective in the treatment of AUD. Randomized clinical trials are urgently needed to confirm whether GLP-1 agonists could be used to treat AUD and SUDs.

## ARTICLE INFORMATION

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**Author Contributions:** Drs Tanskanen and Taipale had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design*: Lähteenvuo, Tiihonen, Tanskanen, Taipale.
*Acquisition, analysis, or interpretation of data*: All authors.
*Drafting of the manuscript*: Lähteenvuo, Solismaa, Taipale.
*Critical review of the manuscript for important intellectual content*: Tiihonen, Solismaa, Tanskanen, Mittendorfer-Rutz, Taipale.
*Statistical analysis*: Tanskanen, Taipale.
*Administrative, technical, or material support*: Tanskanen, Mittendorfer-Rutz.
*Supervision*: Lähteenvuo, Tiihonen.

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# Supplemental Online Content

Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing semaglutide and liraglutide for alcohol use disorder. *JAMA Psychiatry*. Published online November 13, 2024. doi:10.1001/jamapsychiatry.2024.3599



This supplemental material has been provided by the authors to give readers additional information about their work.

**eMethods**

**Exposure**
Exposure was evaluated using the PRE2DUP-method. It uses data from pharmacy dispensings/purchases (dates, amounts and medication type (strength, formulation, etc..)) and turns this data into drug use periods, giving a day-by-day estimate of whether a drug was used or not. The PRE2DUP method is based on the calculation of sliding averages of defined daily dosages, the amounts of drugs purchased, and individual drug use patterns. It takes into account hospital stays and medicine stockpiling. The construction of drug use periods is controlled with clinically meaningful minimum and maximum doses designed for each drug package. It does not use artificial grace periods. It tracks every medication individually and can thus also be used to define polypharmacy[1,2].

**Outcome**
Outcomes were defined based on primary discharge diagnosis of each hospital care period.

**Study design and statistical analysis**
Stratified Cox regression analyses were used to conduct within-individual analyses to calculate the risk of an outcome associated to use versus non-use of pharmacotherapies[3]. In within-individual analysis each individual acts as his/her own control, controlling for bias arising from permanent and semi-permanent characteristics (eFigure 1 and 2). The model is suitable for recurring outcomes, but only individuals with variation in both exposure and outcome directly contribute to the estimation of adjusted hazard ratios. In this study, all individuals exposed to GLP-1 agonists were included in the GLP-1 agonist analysis and all individuals exposed to AUD medications were included in analysis of those, regardless of variation in exposure or having the outcome event (they contributed to analysis indirectly, via time-varying covariates).

Additional analyses were done to control for bias arising from the different market entry times of the medications. In the first analysis, the start of follow-up was defined according to market entry as January 1st 2009 for liraglutide, January 1st 2014 for dulaglutide and January 1st 2018 for semaglutide (eTable 2). In the second analysis, a negative control not likely to affect risk of AUD hospitalization, but with a similar market entry time as for the GLP-1 agonists, was used (eTable 3). For this analysis Sodium-glucose linked transporter-2 (SGLT-2) inhibitors were used as negative controls and start of follow-up was restricted to start when each drug received approval from European Medicines Agency, namely 2012 for dapagliflozin and 2014 for empagliflozin.

The models were adjusted for time-varying use of psychotropic medications (antipsychotics N05A, antidepressants N06A, mood stabilizers including carbamazepine N03AF01, valproic acid N03AG01, lamotrigine N03AX09 and lithium N05AN01), benzodiazepines and related drugs (N05BA, N05CD, N05CF), ADHD medications (N06BA) and use of other antidiabetic drugs than GLP-1 agonists (A10 excluding A10BJ). In addition, the analyses were adjusted for temporal order of GLP-1 agonists and time since cohort entry.

**eReferences**


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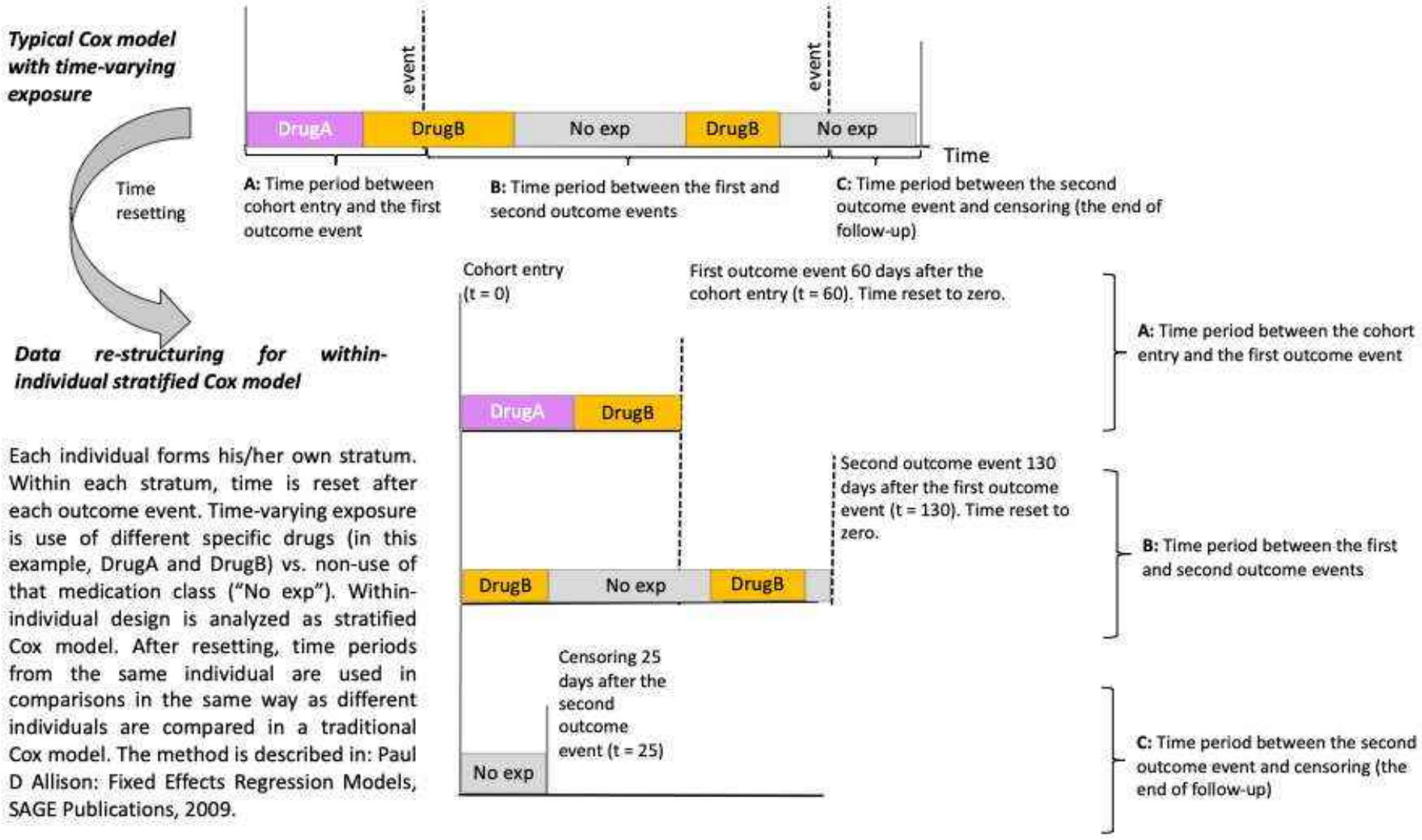
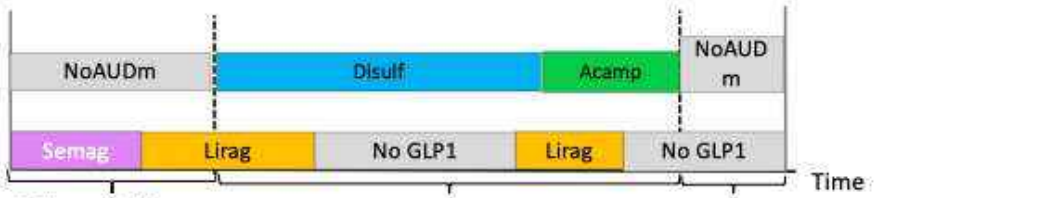
**eTable 1**. **Risk of different outcome events associated with use of medications for alcohol use disorder (AUD) (compared with non-use time of AUD medications) in within-individual model of persons with AUD** (adjusted for time-varying use of psychotropic medications (antipsychotics N05A, antidepressants N06A, mood stabilizers including carbamazepine N03AF01, valproic acid N03AG01, lamotrigine N03AX09 and lithium N05AN01), benzodiazepines and related drugs (N05BA, N05CD, N05CF), ADHD medications (N06BA) and use of other antidiabetic drugs than GLP-1 agonists (A10 excluding A10BJ), temporal order of AUD medication and time since cohort entry).

| | Events | Users | PYs | aHR (95% CI) |
|---|---|---|---|---|
| AUD hospitalization | | | | |
| Disulfiram | 12652 | 44264 | 33134 | 0.98 (0.96-1.00) |
| Acamprosate | 9061 | 31555 | 17575 | 1.11 (1.08-1.15) |
| Naltrexone | 4772 | 31660 | 15032 | 0.86 (0.83-0.89) |
| | | | | |
| SUD hospitalization | | | | |
| Disulfiram | 5673 | 44264 | 33134 | 0.98 (0.96-1.00) |
| Acamprosate | 6250 | 31555 | 17575 | 1.12 (1.09-1.15) |
| Naltrexone | 481 | 31660 | 15032 | 0.86 (0.84-0.90) |
| | | | | |
| Somatic hospitalization | | | | |
| Disulfiram | 50 | 44264 | 33134 | 0.84 (0.81-0.88) |
| Acamprosate | 613 | 31555 | 17575 | 0.94 (0.90-0.99) |
| Naltrexone | 362 | 31660 | 15032 | 0.78 (0.73-0.84) |
| | | | | |
| Suicide attempt | | | | |
| Disulfiram | 1636 | 44264 | 33134 | 1.21 (1.12-1.30) |
| Acamprosate | 699 | 31555 | 17575 | 1.25 (1.10-1.41) |
| Naltrexone | 522 | 31660 | 15032 | 0.95 (0.84-1.09) |

**eFigure 1. Principles of how comparisons are conducted in within-individual design where each individual act as his/her own control**



**eFigure 2. Encoding of variables, exposures and outcomes.**




**A:** Time period between cohort entry and the first outcome event

**B:** Time period between the first and second outcome events

**C:** Time period between the second outcome event and censoring (the end of follow-up)

**Structure of the analyses dataset and variables for the example drug use history above**

| row# | ID | start | stop | GLP | AUD | AD | BE | series | censor | init | end |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | 1 | 29 | Semag | NoAUDm | 1 | 0 | 1 | 0 | 1 | 29 |
| 2 | 3 | 30 | 60 | Lirag | NoAUDm | 1 | 0 | 1 | 1 | 30 | 60 |
| 3 | 3 | 61 | 92 | Lirag | Disulf | 1 | 0 | 2 | 0 | 1 | 32 |
| 4 | 3 | 93 | 98 | NoGLP1 | Disulf | 1 | 0 | 2 | 0 | 33 | 38 |
| 5 | 3 | 99 | 130 | NoGLP1 | Disulf | 0 | 0 | 2 | 0 | 39 | 70 |
| 6 | 3 | 131 | 140 | NoGLP1 | Disulf | 0 | 0 | 2 | 0 | 71 | 80 |
| 7 | 3 | 141 | 146 | Lirag | Disulf | 0 | 0 | 2 | 0 | 81 | 109 |
| 8 | 3 | 147 | 180 | Lirag | Acamp | 0 | 1 | 2 | 0 | 109 | 120 |
| 9 | 3 | 181 | 190 | NoGLP1 | Acamp | 0 | 1 | 2 | 1 | 121 | 130 |
| 10 | 3 | 191 | 215 | NoGLP1 | NoAUDm | 0 | 1 | 3 | 0 | 1 | 25 |

start and stop describe continuous time since cohort entry (start=1) until the end of follow-up (stop=215) as days. These are the basis for between-individual model.

GLP describes time-varying use of two specific GLP-1 agonists (named "Lirag" and "Semag") and non-use of GLP-1 agonists ("No GLP1").

AUD describes the use ("Disulf" and "Acamp") versus non-use of AUD medications ("No AUDm").

Variables AD and BE describe time-varying use of antidepressants and benzodiazepines for which analyses were adjusted for (1=use, 0=non-use). In this study, analysis were also adjusted for the use of antipsychotics, mood stabilizers and ADHD medications which were coded similarly as AD and BE (left out for simplicity, not shown in figure).

series indicates which rows belong to the same series of within-individual model (when series changes time is reset to zero).

censor indicates whether the period ended at outcome event (censor=1) or censoring (censor=0). After censor=1, time is reset and the next row starts with init=1.

init and end assign time variable for within-individual model where time is reset to zero after each outcome event.

**eTable 2. Sensitivity analysis of the main outcome (AUD hospitalization) restricted with years of market approvals for specific GLP-1 agonists analyzed in within-individual model.** Start of follow-up was defined according to market entry as January 1st 2009 for liraglutide, January 1st 2014 for dulaglutide and January 1st 2018 for semaglutide.

| | Events | Users | PYs | aHR (95%CI) |
|---|---|---|---|---|
| Liraglutide since 2009 | | | | |
| Non-use of GLP-1 agonists | 9367 | 6252 | 58462 | |
| Liraglutide | 212 | 2509 | 3076 | 0.73 (0.58-0.92) |
| Dulaglutide since 2014 | | | | |
| Non-use of GLP-1 agonists | 4872 | 6234 | 42468 | |
| Dulaglutide | 139 | 1118 | 1443 | 0.95 (0.67-1.33) |
| Semaglutide since 2018 | | | | |
| Non-use of GLP-1 agonists | 2572 | 6142 | 25618 | |
| Semaglutide | 222 | 4321 | 4677 | 0.68 (0.51-0.89) |

**eTable 3. Risk of AUD hospitalization associated with Sodium-glucose linked transporter-2 (SGLT-2) inhibitor use, compared to non-use of SGLT-2 inhibitors in within-individual model.**

| | Events | Users | PYs | aHR (95%CI) | Time-restricted aHR (95%CI)* |
|---|---|---|---|---|---|
| Non-use of SGLT-2 inhibitors | 13009 | 6970 | 67164 | reference | reference |
| Dapagliflozin | 414 | 2838 | 3555 | 1.00 (0.76-1.33) | 1.07 (0.80-1.42) |
| Empagliflozin | 630 | 4452 | 7961 | 0.84 (0.64-1.09) | 0.88 (0.67-1.16) |

*Start of follow-up restricted by time when each drug received approval from European Medicines Agency, namely 2012 for dapagliflozin and 2014 for empagliflozin.

**eAppendix**

*Study strengths and weaknesses*

The strengths of this study include a large and inclusive cohort analyzed with validated methods. However, as this is an observational study, it can only speak for associations, not causality, and possible mechanisms behind the associations are beyond reach for this study. The within-individual analysis used eliminates bias arising from permanent or semi-permanent characteristics. Some forms of biases still remain. Firstly, we could not ascertain for what diagnosis the GLP-1 agonists were initially prescribed for. They may have different effects for individuals suffering from diabetes or obesity or both. This study was not able to obtain data on amount or activity of substance use, and thus all outcomes used are merely proxies, although do represent very meaningful and concrete consequences. Also, this study could not account for benefits/problems not showing up in registries, such as a decrease in amounts consumed or improvement in quality of life or daily functioning. Also, SUDs may have different stages. The effect of medications may be different whether they are started during periods of abstinence or active use, but this study was unable to control for this effect. Also, the analysis assumes that changes in exposure should not be dependent on outcomes. This is likely true for the analyses for GLP-1 agonists, but hospitalizations due to AUD may have modified the risk of a patient receiving an AUD medication prescription, which may have introduced some bias to the results presented for AUD-medications, possibly leading to the underestimation of their effectiveness. Another underlying assumption of the model is that outcomes are independent. It is possible that being hospitalized for an AUD can affect the willingness of a patient to seek further hospitalizations in the future, either reducing or increasing this willingness, which may also have led to bias.

# Data Sharing Statement

Lähteenvuo. Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder. *JAMA Psychiatry*. Published November 13, 2024. doi:10.1001/jamapsychiatry.2024.3599

**Data**
**Data available:** No

**Additional Information**
**Explanation for why data not available:** The data used in this study cannot be made publicly available due to privacy regulations. According to the General Data Protection Regulation, the Swedish law SFS 2018:218, the Swedish Data Protection Act, the Swedish Ethical Review Act, and the Public Access to Information and Secrecy Act, these types of sensitive data can only be made available for specific purposes, including research, that meets the criteria for access to this sort of sensitive and confidential data as determined by a legal review. Readers may contact Professor Kristina Alexanderson (kristina.alexanderson@ki.se) regarding the data.