Once-weekly semaglutide versus placebo in patients with alcohol use disorder and comorbid obesity: a randomised, double-blind, placebo-controlled trial

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Summary

Background Alcohol use disorder accounts for 5% of deaths worldwide annually, and there is an urgent need for new therapeutic interventions. Preclinical and initial human studies indicate that the GLP-1 receptor agonist semaglutide might reduce alcohol drinking. This study evaluated the efficacy of semaglutide once-weekly in treatment-seeking patients with alcohol use disorder and comorbid obesity.

Methods In a 26-week, single-centre, randomised, double-blinded, placebo-controlled trial, treatment-seeking participants with moderate to severe alcohol use disorder and comorbid obesity were assigned (1:1) to receive once-weekly semaglutide (2·4 mg subcutaneously) or placebo (saline subcutaneously), in addition to standard cognitive behavioural therapy. The primary endpoint was a reduction in the number of heavy drinking days assessed after 26 weeks of intervention, analysed with an ANCOVA model. Analysis adhered to the intention-to-treat principle, and missing outcome data were addressed using multiple imputations. Safety was assessed in all treated patients. The trial is registered at ClinicalTrials.gov NCT05895643, and is complete.

Findings From June 10, 2023, to Feb 4, 2025, 108 participants (53 women and 55 men) were enrolled, with 54 participants in each of the semaglutide and placebo treatment groups, and all were included in the data analysis. Overall, 88 participants (81%) completed the full intervention. Semaglutide was associated with a reduction in heavy drinking days (–41·1 percentage points from baseline, 95% CI –48·7 to –33·5) compared with placebo (–26·4, –34·1 to –18·6; estimated treatment difference –13·7 percentage points, –22·0 to –5·4; p=0·0015), and had substantial effects on multiple secondary alcohol-related and somatic outcomes. Adverse events were transient, generally mild to moderate gastrointestinal effects, and occurred more frequently in the semaglutide group.

Interpretation Semaglutide showed robust therapeutic effects in treatment-seeking participants with obesity and alcohol use disorder and this trial supports previous preclinical and clinical findings suggesting GLP-1 receptor agonists as a potential novel treatment target for alcohol use disorder.

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Introduction

Alcohol use disorder is a chronic, relapsing brain disorder characterised by loss of control of alcohol consumption and compulsive use.[1] Several behavioural and psychological treatments are available,[1] and cognitive behavioural therapy (CBT) is among the treatments with the highest empirical support.[2] However, despite decades of research, the US Food and Drug Administration (FDA) has approved only three medications—disulfiram, acamprosate, and naltrexone[1]—highlighting the urgent need for more effective treatments. GLP-1 receptor agonists, approved for the treatment of diabetes and obesity,[3] have gained wide attention for their effects on brain pathways involved with appetite regulation and reward, suggesting potential use for mitigating alcohol consumption.[4] Importantly, GLP-1 receptor agonists are generally well tolerated and have a favourable safety profile, with a low risk of hypoglycaemia due to their glucose-dependent mechanism.[5] The endogenous GLP-1-peptide is secreted from L-cells in the small intestine and also synthesised in brain areas implicated in reward and addiction.[6]

Several GLP-1 receptor agonists have shown significant reductions in alcohol consumption, reward-processing, and relapse-like behaviours, demonstrating robust and promising effects in preclinical models of alcohol addiction.[7,8] In humans, register-based studies have reported a lower risk of alcohol-related events or alcohol use disorder diagnosis among individuals treated with a GLP-1 receptor agonist.[9] Recently, a randomised

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Research in context

Evidence before this study

No formal literature review was done before commencing this study; however, we previously published a Review on GLP-1 in addictive disorders in 2022. Alcohol use disorder is a chronic brain disorder marked by loss of control over drinking and compulsive use. Despite decades of research, only three medications are approved for alcohol use disorder, underscoring the need for novel treatments. GLP-1 receptor agonists, established therapies for diabetes and obesity, have gained wide attention for their effects on reward pathways and appetite regulation, suggesting potential use in mitigating alcohol consumption. GLP-1 receptor agonists have shown promising results in preclinical models of alcohol addiction. In humans, register-based studies have reported a lower risk of alcohol-related events or alcohol use disorder diagnosis among individuals with diabetes or obesity treated with a GLP-1 receptor agonist. At the time of study initiation, only one randomised controlled trial (RCT) of GLP-1 receptor agonists in treatment-seeking patients with alcohol use disorder showed no overall effect on heavy drinking days. However, reductions were observed among participants with a BMI greater than 30 kg/m², along with decreased activation to alcohol cues in reward-related brain regions, suggesting reduced incentive salience. More recently, an RCT investigating the efficacy of the GLP-1 receptor agonist semaglutide in a low dose in 48 non-treatment-seeking individuals with alcohol use disorder showed a significant reduction in alcohol intake in a laboratory self-administration task. To our knowledge to date, no other RCTs in treatment-seeking individuals have been published.

Added value of this study

This randomised, double-blind, placebo-controlled clinical trial shows, for the first time, to our knowledge, that the GLP-1 receptor agonist semaglutide at 2·4 mg once-weekly reduces alcohol consumption in treatment-seeking patients with alcohol use disorder and comorbid obesity (BMI ≥30 kg/m²).

Implications of all the available evidence

These data, when added to the growing evidence, demonstrate the potential of GLP-1 receptor agonists as a novel treatment for alcohol use disorder. However, corroboration with larger RCTs in patients without obesity is needed to address its generalisability.

See Online for appendix 1

controlled trial (RCT) that included 48 non-treatment-seeking participants with alcohol use disorder[10]—characterised by lower alcohol use disorder severity, fewer alcohol-related consequences, and less motivation to reduce alcohol consumption[11]—received low-dose semaglutide for 2 months. The study showed a significant reduction in alcohol consumption in a laboratory-based alcohol self-administration task, and decreases in drinks per drinking day and alcohol craving, compared with placebo.[10] To our knowledge, only one RCT has evaluated the effects of a GLP-1 receptor agonist (once-weekly exenatide) in treatment-seeking patients with alcohol use disorder.[12] No overall

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difference in the number of heavy drinking days was observed, but an exploratory analysis showed that exenatide reduced alcohol consumption in participants with a BMI above 30 kg/m². In a subset of participants undergoing functional MRI, treatment with exenatide compared with placebo decreased reactivity to alcohol cues in reward-related brain areas.[12] Consequently, we

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conducted a 26-week RCT in treatment-seeking patients with obesity and alcohol use disorder, aiming to investigate the effect and safety of the GLP-1 receptor agonist semaglutide, 2·4 mg subcutaneously once-weekly, on alcohol consumption.

Methods

Study design

This randomised, single-centre, double-blinded, placebo-controlled, clinical trial was carried out at the Mental Health Center Copenhagen, Copenhagen, Denmark. The protocol (appendix 1) was approved by the Ethics Committee of the Capital Region of Denmark and the Danish National Board of Health (EU CT NUMBER: 2023-503371-25-00), and the Danish Data Protection Agency (P-2023–187). Data were collected and managed using the REDCap.[13] The trial was conducted in accordance with the Declaration of Helsinki. Independent good clinical practice (GCP) monitoring was provided by the regional GCP unit, ensuring compliance with International Council for Harmonisation (ICH)-GCP guidelines, integrity of trial data, safety evaluations, and applicable regulatory requirements No patients were involved in the design, conduct, or reporting of the trial. Appendix 1 contains the full protocol, and appendix 2 (p 4) contains minor protocol amendments and minor protocol deviations. The trial is registered at ClinicalTrials.gov (NCT05895643), and is complete.

Participants

Participants were recruited via advertisements on a trial webpage and a patient recruitment service advertising on social media, which were approved by the authorities. Before the screening session, a 20-min telephone interview was conducted, including an assessment of treatment-seeking status (eg, seeking help to obtain professional help to reduce, control, or stop alcohol use). Eligible participants were alcohol use disorder treatment-seeking and age 18–70 years. At the screening session, a diagnostic interview was performed by a medical doctor, and an alcohol use disorder diagnosis was given according to the Diagnostic and Statistical Manual of Mental

Disorders, 5th edition (DSM-5), and alcohol dependence according to the ICD-10. All participants had a BMI of 30 kg/m² or higher, an alcohol use disorders identification test (AUDIT) score above 15, and a minimum of 6 heavy drinking days, (ie, ≥60 g for men or ≥48 g for women of alcohol per day) during 30 days as estimated using the validated, gold-standard tool, the Timeline Followback (TLFB) method.[14] Key exclusion criteria were severe mental disorder, other substance use disorders (other than tobacco), a history of diabetes, pancreatitis, or alcohol withdrawal seizures, and current use of medications targeting alcohol use disorder. A full list of inclusion and exclusion criteria is provided in appendix 2 (p 5). All participants were informed of their rights both verbally and in writing by a medical doctor and were required to have a breath alcohol concentration below 0·5‰, before providing written informed consent. Data on gender (male, female, or other) and ethnicity were obtained through participant self-reporting. In accordance with Danish law, no participants received financial incentives to remain in the trial.

Randomisation and masking

Randomisation used a block design, with block sizes of two and four, stratified by sex assigned at birth, age (two strata with a cutoff at 40 years), and number of heavy drinking days at baseline (four strata). Before trial initiation, personnel not involved in other trial activities generated the allocation sequence using Sealed Envelope and uploaded it to the REDCap[13] randomisation module, which implemented the computer-generated block randomisation sequence to ensure balanced allocation across groups. Upon enrolment, participants were automatically assigned 1:1 in the REDCap system, to receive either once-weekly, subcutaneous semaglutide (2·4 mg) or placebo (saline). The automatic assignment was performed by unmasked personnel who were not involved in other trial activities.

Participants attended weekly sessions to receive the assigned treatment, administered by an unmasked nurse. Participants were wearing blindfolds and headphones, listening to music, to mask a potential audible click sound from the semaglutide subcutaneous injection pen. Placebo injections were administered subcutaneously and matched semaglutide in volume and needle size. CBT and assessments were performed by masked personnel, and analyses were conducted by a masked external statistician.

Procedures

Semaglutide was supplied by the Pharmacy of the Capital Region of Copenhagen as prefilled FlexTouch pen injectors (Wegovy [Novo Nordisk]) in doses of 0·25 mg, 0·5 mg, 1·0 mg, 1·7 mg, and 2·4 mg. Placebo consisted of prefilled saline syringes (BD PosiFlush [Becton Dickinson]). Participants initiated treatment with subcutaneous semaglutide 0·25 mg once-weekly, with dose escalation every 4 weeks in accordance with the manufacturer's recommendations, until the maximum tolerated dose or the target dose of 2·4 mg was reached, or placebo in equivalent dose. All participants were offered up to ten standardised CBT sessions delivered by a trained nurse, lasting 45 min, and focused on motivation, craving, strategies, permissive cognitions, and relapse prevention regarding alcohol use. No nutritional counselling was provided, and monitoring of nutritional deficiencies was restricted to assessments of vitamin D and vitamin B12 at weeks 0 and 26, with supplementation recommended for low levels. Regular assessments, including TLFB evaluations and blood sampling were performed in person and by personnel masked to treatment assignment at the research facility (a detailed schedule is shown in appendix 2 pp 6–7). Women of childbearing potential were required to use effective contraception for the duration of the trial and underwent pregnancy testing at baseline and if pregnancy was suspected. A follow-up telephone call to each participant was conducted by a medical doctor 5 weeks after the end of trial participation to assess any safety concerns. All eligible participants were invited to a brain imaging substudy, with MRI scans conducted before the first injection and again at 26 weeks. Imaging data will be reported elsewhere. The full protocol has been published.[15]

Outcomes

The primary endpoint was the change in heavy drinking days from baseline to week 26, estimated by the TLFB method.[14] Previous experience recruiting participants with alcohol use disorder has shown that an initial telephone screening can lead to reductions in alcohol consumption.[12,16] To mitigate this potential bias, baseline alcohol use was assessed based on a consecutive 30-day period with the highest alcohol consumption—defined as the period with the largest number of heavy drinking days and subsequently the greatest total alcohol intake—selected from the 40 days preceding enrolment. This approach was a pragmatic way to mitigate potential bias in the baseline assessment and to obtain a baseline measure that more closely reflects pre-enrolment drinking behaviour. Importantly, the same procedure was applied at all subsequent assessments (weeks 6, 12, 20, and 26), ensuring consistency across all timepoints, and ensuring that results will still be comparable to other studies. Secondary endpoints were—from baseline to week 26—changes in total alcohol consumption (g), number of days without alcohol consumption, number of drinks per drinking day, alcohol craving (Penn alcohol craving scale [PACS] score), screen for harmful alcohol use (AUDIT and AUDIT for consumption[-C] scores), time to relapse, WHO risk drinking levels, screen for harmful drug use (drug use disorders identification test [DUDIT] score), Fagerström Test for Nicotine Dependence (FTND) score, plasma liver enzymes (γ-glutamyl transferase and alanine aminotransferase), plasma mean cell volume,

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plasma phosphatidyl ethanol, Fibrosis-4 Index for Liver Fibrosis score, glycated haemoglobin (HbA_{1c}), bodyweight (kg), blood pressure (systolic and diastolic, mm Hg), pulse (beats per min), waist circumference (cm), and measures of health and life quality (WHO quality of life brief [QOL-BREF] questionnaire score). A reference list of assessment instruments is available in appendix 2 (p 8). Adverse events were evaluated non-systematically at the scheduled visits and by self-reporting. For each type of event, the number and percentage of participants who had that event at least once were presented by treatment group.

Statistical analysis

The sample size was based on an RCT investigating psilocybin-assisted therapy for alcohol use disorder, which showed a 47 percentage point reduction in heavy drinking days in the intervention group versus 25 percentage points in the placebo group.[17] Assuming 90% power, a two-sided alpha of 0·05, and an estimated standard deviation of 26·4 percentage points, we calculated that 64 participants would be required. Because dropout rates of 10–35% are common in clinical alcohol use disorder trials,[18] we anticipated a 40% attrition rate and set the target sample size at 108 participants (54 per group). Analysis adhered to the intention-to-treat principle, including all randomised participants who received their first injection. The primary endpoint—change in the percentage of heavy drinking days from baseline to week 26, adjusted for baseline—was analysed using baseline-adjusted ANCOVA. Secondary endpoints were analysed using ANCOVA models for continuous outcomes and Cox proportional hazards models for time-to-event outcomes. Subgroup analyses were prespecified for baseline heavy drinking days (days 6–11, 12–17, 18–23, and 24–30) and DSM-5 severity (mild, moderate, and severe). Missing outcome data were addressed using multiple imputation by predictive mean matching, based on all available repeated measures for each endpoint. This approach assumed that outcome data were missing at random in the sense that the probability of missingness depended on observed data, but not the missing values themselves. In the context of this trial, missingness could be due to loss to follow-up or withdrawal, factors expected to be related to baseline drinking patterns, but possibly also to the actual endpoint values. Thus, since the missing at random assumption cannot be formally tested, pre-planned sensitivity analyses were conducted under more conservative scenarios: (1) complete-case analysis including only individuals with values observed at both baseline and endpoint, (2) imputing missing outcome values at week 26 as a return to baseline levels, and (3) imputing missing outcome values at week 26 as 50% reduction from baseline. In addition, Cohen's *d* effect size, which quantifies the magnitude of the difference between two means relative to the total variability in data, was calculated for the endpoints of number of heavy drinking days, total alcohol consumption, and number of drinks per drinking day. Spearman's rank correlation test was used to assess the relationship between weight loss and the endpoints of heavy drinking days and total alcohol consumption. All tests were two-sided with a significance level of 0·05, and 95% CIs were reported for estimated treatment differences. No multiplicity adjustments were performed, and no additional covariate adjustments were applied, except for the endpoint's baseline value. However, for the primary endpoint, an additional analysis adjusted for sex assigned at birth, age (two levels, age 40 years as a cutoff), and number of heavy drinking days at baseline (four levels) was provided. The model fit was evaluated visually using Q–Q plots and residual plots based on a randomly selected imputed dataset. No substantial model deviations were observed. However, as a precaution, a sensitivity analysis using the Huber–White sandwich estimator to make inferences more robust to potential model misspecification was done. No interim analyses were done. Analyses were performed in R (version 4.3.2). No data monitoring committee was established; this was a small, single-centre study, without pharmaceutical industry involvement, and with investigators who saw participants on a regular basis. The statistical analysis plan (appendix 1) was uploaded to ClinicalTrials.gov a priori, and the dataset was locked before analysis.

Role of the funding source

The funding sources and the manufacturer of semaglutide once-weekly (Wegovy) had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 10, 2023, to Feb 4, 2025, 302 participants were pre-screened for eligibility; of the 135 participants screened, 108 were enrolled and received at least one injection, and were included in the final analysis (54 per group; table 1). In total, 88 participants (81%) completed the trial (figure 1). There was no significant difference in time to trial discontinuation between the two groups (and the p value was not adjusted), with 14 patients in the placebo group discontinuing by week 26 compared with six in the semaglutide group (hazard ratio [HR] 0·39, 95% CI 0·15–1·01; appendix 2 p 12).

Baseline analysis showed a gender distribution of 53 (49%) women and 55 (51%) men overall, and a mean age of 52·3 years (SD 9·8). The 108 participants had a mean of 17·2 heavy drinking days (SD 7·8), an overall alcohol intake of 2200·9 g (SD 1128·0) of pure alcohol over the last 30 consecutive days, an overall AUDIT score of 22·8 (SD 4·4), and 92 (85%) fulfilled the criteria for severe alcohol use disorder according to DSM-5.

For the primary endpoint, participants treated with semaglutide had greater reductions in the number of heavy drinking days compared with the placebo group. The mean change was –41·1 percentage points (95% CI –48·7 to –33·5) for the semaglutide group versus

	Placebo (n=54)	Semaglutide (n=54)
Sex assigned at birth*		
Male	28 (52%)	27 (50·0)
Female	26 (48%)	27 (50·0)
Age		
Mean age, years	51·7 (9·8)	52·8 (9·8)
40 years and younger*	6 (11%)	5 (9%)
Older than 40 years*	48 (89%)	49 (91%)
Cohabiting or married	29 (54%)	22 (41%)
Race or ethnicity		
Asian	0	4 (7%)
Black or African American	1 (2%)	1 (2%)
White	53 (98%)	49 (91%)
Employed	40 (74%)	39 (72%)
Education		
Lower secondary school	3 (6%)	3 (6%)
Upper secondary school	2 (4%)	2 (4%)
Vocational education or short-cycle higher education	21 (39%)	14 (26%)
Medium-cycle higher education or higher education	28 (52%)	35 (65%)
Previous treatment with a glucagon-like peptide-1	8 (15%)	5 (9%)
Previous pharmacological treatment for alcohol use disorder		
Disulfiram	9 (17%)	10 (19%)
Acamprosate	5 (9%)	5 (9%)
Naltrexone	1 (2%)	1 (2%)
Nalmefene	0	0
Alcohol use disorders identification test score†	22·3 (4·5)	23·2 (4·3)
Alcohol use disorders identification test consumption score‡	9·8 (1·3)	9·7 (1·2)
ICD-10: alcohol dependence		
3 symptoms	5 (9%)	2 (4%)
4 symptoms	32 (59%)	26 (48%)
5 symptoms	13 (24%)	21 (39%)
6 symptoms	4 (7%)	5 (9%)
Diagnostic and Statistical Manual of Mental Disorders, 5th edition: alcohol use disorder		
Mild (2–3 symptoms)	0	0
Moderate (4–5 symptoms)	11 (21%)	5 (9%)
Severe (>5 symptoms)	43 (80%)	49 (91%)
(Continued from previous column)		
Heavy drinking days§	17·2 (7·4)	17·1 (8·2)
Heavy drinking days randomisation strata		
6–11 days*	15 (28%)	17 (32%)
12–17 days*	14 (26%)	14 (26%)
18–23 days*	10 (19%)	7 (13%)
24–30 days*	15 (28%)	16 (30%)
Days without alcohol consumption	8·5 (7·3)	9·1 (7·5)
Total alcohol consumption, g of alcohol per 30 days§	2246·6 (1091·9)	2155·3 (1171·5)
Phosphatidyl ethanol, µmol/L	0·7 (0·6)	0·5 (0·5)
WHO risk drinking level¶		
Low	1 (1·9%)	1 (1·9%)
Medium	12 (22·6%)	16 (29·6%)
High	23 (42·6%)	19 (35·2%)
Very high	18 (33·3%)	18 (33·3%)
Fagerströms test for Nicotine Dependence score‖	4·2 (2·8)	3·5 (2·5)
Cigarettes per day	14·9 (10·1)	13·2 (9·5)
Bodyweight, kg	105·2 (15·5)	100·3 (12·0)
BMI, kg/m²	35·2 (4·4)	33·7 (3·3)
Glycated haemoglobin**	5·4 (0·4)	5·5 (0·3)

Data are n (%) or mean (SD). *Randomisation strata. †Total score ranges from 0 to 40, with higher scores reflecting higher alcohol dependence. ‡Subscale with total score ranging from 0 to 12 focusing solely on alcohol consumption patterns. §The 30 consecutive days with highest alcohol use (most heavy drinking days and greatest total intake) within the 40 days before evaluation, measured by the Timeline Followback method. ¶Low risk: 1–40 g/day for men, 1–20 g/day for women; moderate risk: 41–60 g/day for men, 21–40 g/day for women; high risk: 61–100 g/day for men, 41–60 g/day for women; very high risk: >100 g/day for men, >60 g/day for women. ‖Only individuals who reported current smoking at baseline (n=31; placebo n=15 and semaglutide n=16) were included; the number of daily cigarettes were self-reported at baseline. **To convert glycated haemoglobin from percentage to mmol/mol, subtract 2·15 and multiply by 10·929.

Table 1: **Baseline characteristics**

–26·4 percentage points (–34·1 to –18·6) for the placebo group, corresponding to a mean difference of –13·7 percentage points (95% CI –22·0 to –5·4; p=0·0015; table 2, figure 2A).

For the secondary alcohol consumption outcomes, semaglutide led to greater improvements than in those receiving placebo across multiple measures. Mean total alcohol consumption decreased (–1550·2 g/30 days with semaglutide *vs* –1025·9 g/30 days with placebo; estimated difference –467·5 g/30 days [95% CI –739·5 to –195·4]; figure 2B) and mean drinks per drinking day (–3·5 units *vs* –2·1 units; estimated difference –1·5 units [–2·6 to –0·5]). Improvements were also seen in mean PACS score (–9·2 *vs* –6·1; estimated difference –3·1 [–5·1 to –1·2]), mean AUDIT score (–9·9 *vs* –6·3; estimated difference –3·3 [–5·5 to –1·1]), mean AUDIT-C score (–4·2 *vs* –2·7; estimated difference –1·5 [–2·6 to –0·4]), and overall WHO risk drinking levels (–1·75 *vs* –1·24; estimated difference –0·52 [–0·89 to –0·16]; table 2). The semaglutide group also had a significant 2-level reduction in the WHO risk drinking level compared with the placebo group (appendix 2 p 9).

Analysis of biomarkers also showed favourable changes with semaglutide, including plasma phosphatidyl ethanol (–0·24 µmol/L with semaglutide *vs* 0·00 µmol/L with placebo; estimated difference –0·28 [–0·41 to –0·15]; appendix 2 p 12), γ-glutamyl transferase (–36·0 U/L *vs* –10·2 U/L; estimated difference –24·2 [–33·4 to –15·1]), and plasma mean cell volume (–1·3 fL *vs* 0·4 fL; estimated

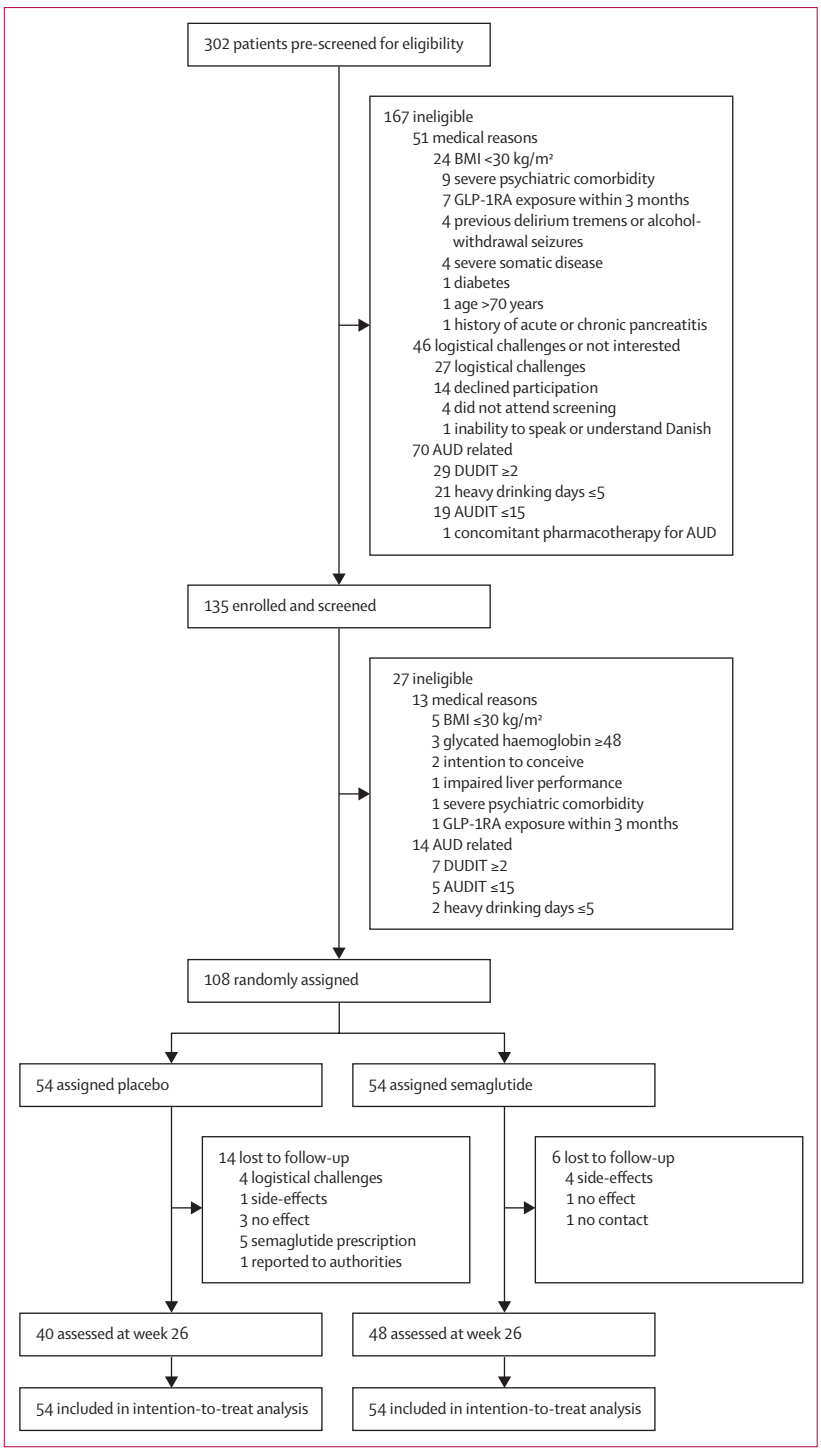

Figure 1: **Trial profile**
Pre-screenings conducted via telephone. AUD=alcohol use disorder. AUDIT=alcohol use disorders identification test. DUDIT=drug use disorders identification test. GLP-1RA=glucagon-like peptide-1 receptor agonist.

difference –1·7 [–2·6 to –0·7]; table 2). Elevated amylase was found in the semaglutide group (4·7 U/L *vs* –0·9 U/L in the placebo group; 5·1 [2·5–7·7]; table 2), and four participants had asymptomatic elevations of amylase above upper limit, with the highest value recorded as 123 U/L (normal range 10–65 U/L; table 3). Other biomarkers did not significantly differ between groups (table 2).

Analysis of metabolic measures showed favourable changes of semaglutide, with regard to bodyweight (–11·2 kg with semaglutide *vs* –2·2 kg with placebo; estimated difference –9·0 [–11·2 to –6·7]; appendix 2 p 13), mean percent change in bodyweight (–11·36% *vs* –2·0%; estimated difference –9·0 [–11·3 to –6·8]), waist circumference (–12·1 cm *vs* –3·8 cm; estimated difference –8·3 [–11·2 to –5·4]), BMI (–3·8 *vs* –0·7; estimated difference –3·1 [–3·8 to –2·3]), and HbA_{1c} (–0·3% *vs* 0·0%; estimated difference –0·3 [–0·4 to –0·2]). Other metabolic measures did not significantly differ between groups (table 2).

Analysis of patient-reported outcomes from the WHOQOL-BREF questionnaire showed that semaglutide improved self-evaluated general health (0·98 with semaglutide *vs* 0·26 with placebo; estimated difference 0·48 [0·13–0·83]) and psychological health (3·86 *vs* 1·81; estimated difference 1·51 [0·15–2·88] appendix 2 p 9), but there was no improvement in overall quality of life or physical health. A sensitivity analysis using the Huber–White sandwich estimator was done: across the 100 imputations, the use of the sandwich estimator resulted in an average increase in confidence interval widths of 0·29, which did not change the overall conclusion.

In our prespecified subgroup analyses, a significant effect of semaglutide on the reduction in heavy drinking days was detected in the subgroup who reported 12–17 heavy drinking days at baseline compared with the placebo group (–38·7 with semaglutide *vs* –16·7 with placebo; estimated difference –22·7 [–33·3 to –12·2]) and in the subgroup having severe alcohol use disorder (–43·2 *vs* –26·9; estimated difference –12·0 [–19·4 to –4·6]; appendix 2 p 10). The interpretation of these subgroup results is addressed in the Discussion. A post-hoc sensitivity analysis of the primary endpoint, adjusted for sex, age, and number of heavy drinking days at baseline, showed the robustness of the results (appendix 2 p 8).

The most common adverse events reported were gastrointestinal symptoms, with a higher incidence in the semaglutide group compared with the placebo group (nausea in 31 [57%] of 54 patients *vs* four [7%] of 54; loss of appetite in 19 [35%] *vs* eight [15%]; food aversion in 13 [24%] *vs* one [2%]; vomiting in eight [15%] *vs* one [2%]; abdominal pain in 11 [20%] *vs* four [7%]; constipation in 19 [35%] *vs* nine [17%]; and reflux in 15 [28%] *vs* one [2%]), and fatigue (17 [32%] of 54 patients *vs* ten [19%] of 54; table 3). The gastrointestinal side-effects reported were mainly mild to moderate and transient; however, five participants (four in the semaglutide group) discontinued the trial due to side-effects.

	Placebo (n=54)	Semaglutide (n=54)	Estimated treatment difference, placebo *vs* semaglutide (95% CI)	p value
Self-reported drinking and alcohol scales				
Heavy drinking days, percentage points (primary endpoint)*	−26·4 (−34·1 to −18·6)	−41·1 (−48·7 to −33·5)	−13·7 (−22·0 to −5·4)	0·0015
Total alcohol consumption, g/30 days*	−1025·9 (−1260·0 to −791·1)	−1550·2 (−1868·2 to −1232·1)	−467·5 (−739·5 to −195·4)	<0·0009
Days without alcohol consumption, percentage points*	27·6 (19·8–35·5)	38·9 (30·6–47·3)	10·1 (−0·0 to 20·2)	0·051
Change in drinks per drinking day*	−2·1 (−3·1 to −1·1)	−3·5 (−4·5 to −2·6)	−1·5 (−2·6 to −0·5)	0·0051
Reduction in WHO risk drinking levels†	−1·24 (−1·54 to −0·94)	−1·75 (−2·04 to −1·45)	−0·52 (−0·89 to −0·16)	0·0055
Alcohol craving (Penn alcohol craving scale score)‡	−6·1 (−7·6 to −4·6)	−9·2 (−10·8 to −7·6)	−3·1 (−5·1 to −1·2)	0·0020
Alcohol use disorders identification test score§	−6·3 (−7·8 to −4·7)	−9·9 (−11·6 to −8·2)	−3·3 (−5·5 to −1·1)	0·0044
Alcohol use disorders identification test consumption score¶	−2·7 (−3·4 to −1·9)	−4·2 (−5·0 to −3·5)	−1·5 (−2·6 to −0·4)	0·0071
Alcohol biomarkers				
Phosphatidyl ethanol, µmol/L	0·00 (−0·10 to 0·11)	−0·24 (−0·34 to −0·13)	−0·28 (−0·41 to −0·15)	<0·0001
Liver and pancreas parameters				
Alanine aminotransferase, U/L	−6·5 (−11·0 to −2·0)	−12·5 (−21·2 to −3·9)	−3·3 (−11·0 to 4·4)	0·40
γ-glutamyl transferase, U/L	−10·2 (−17·5 to −2·9)	−36·0 (−52·2 to −19·7)	−24·2 (−33·4 to −15·1)	<0·0001
Mean corpuscular volume, fL	0·4 (−0·6 to 1·1)	−1·3 (−1·9 to −0·6)	−1·7 (−2·6 to −0·7)	0·0007
Amylase, U/L	−0·9 (−2·7 to 1·0)	4·7 (2·8 to 6·6)	5·1 (2·5 to 7·7)	0·0002
FIB-4‖	0·0 (−0·1 to 0·1)	−1·1 (−3·2 to 1·0)	0·0 (−0·1 to 0·2)	0·67
Clinical measures				
Bodyweight, kg	−2·2 (−3·7 to −0·6)	−11·2 (−12·9 to −9·6)	−9·0 (−11·2 to −6·7)	<0·0001
Bodyweight, %	−2·0 (−3·4 to −0·5)	−11·36 (−13·0 to −9·7)	−9·0 (−11·3 to −6·8)	<0·0001
Systolic blood pressure, mm Hg	−10·6 (−16·2 to −5·0)	−14·5 (−19·8 to −9·2)	−6·8 (−13·5 to −0·1)	0·047
Diastolic blood pressure, mm Hg	−4·5 (−7·7 to −1·3)	−5·6 (−8·8 to −2·4)	−2·1 (−5·7 to 1·6)	0·26
Pulse, beat per min	2·7 (−0·8 to 6·2)	1·8 (−1·3 to 5·0)	−0·7 (−4·8 to 3·4)	0·74
Waist circumference, cm	−3·8 (−6·0 to −1·5)	−12·1 (−14·2 to −10·0)	−8·3 (−11·2 to −5·4)	<0·0001
BMI, kg/m²	−0·7 (−1·2 to −0·2)	−3·8 (−4·4 to −3·2)	−3·1 (−3·8 to −2·3)	<0·0001
Glucose metabolism				
Glycated haemoglobin**, %	0·0 (−0·0 to 0·0)	−0·3 (−0·4 to −0·2)	−0·3 (−0·4 to −0·2)	<0·0001
Other drugs				
Drug use disorders identification test score††	0·2 (−0·1 to 0·5)	0·1 (−0·1 to −0·2)	−0·1 (−0·4 to 0·3)	0·77
FTND score‡‡	−0·7 (−1·6 to 0·3)	−0·1 (−0·6 to 0·4)	0·3 (−0·9 to 1·5)	0·60
Number of cigarettes per day‡‡	−1·8 (−3·5 to −0·1)	−2·5 (−5·6 to 0·7)	−0·5 (−3·7 to 2·7)	0·75

Data are mean (95% CI) unless otherwise stated. FIB-4=fibrosis-4 index. FTND=Fagerströms test for nicotine dependence. *The 30 consecutive days with highest alcohol use (most heavy drinking days and greatest total intake) within the 40 days before evaluation, measured by the Timeline Followback method. †Low risk: 1–40 g/day for men, 1–20 g/day for women; moderate risk: 41–60 g/day for men, 21–40 g/day for women; high risk: 61–100 g/day for men, 41–60 g/day for women; very high risk: >100 g/day for men, >60 g/day for women. ‡Total scores ranges from 0 to 30, with higher scores reflecting higher alcohol craving. §Total scores range from 0 to 40, with higher scores reflecting greater likelihood of alcohol-related problems. ¶Subscale with total score ranging from 0 to 12 focusing solely on alcohol consumption patterns. ‖FIB-4=(age × aspartate aminotransferase) / (platelets × √alanine aminotransferase); non-invasive liver fibrosis estimate, higher scores indicate greater risk. ** To convert glycated haemoglobin from percentage to mmol/mol, subtract 2·15 and multiply by 10·929. ††Total score ranges from 0 to 44, with higher scores indicating greater likelihood of drug-related problems. ‡‡Only individuals who reported current smoking at baseline (n=31; placebo n=15 and semaglutide n=16) were included; a lower FTND score indicates lower nicotine dependence; the number of daily cigarettes were self-reported at baseline and at week 26.

Table 2: **Change in endpoints from baseline to week 26**

The only serious adverse event recorded in the semaglutide group was one hospital admission due to abdominal pain (semaglutide 0·25 mg), without trial discontinuation. In the placebo group, one participant was admitted for alcohol withdrawal symptoms, one participant was treated at hospital for an eye issue, and one patient was admitted for acute coronary syndrome observation, without trial discontinuation (table 3). No other participants had treatment-requiring alcohol withdrawal symptoms. By the 5-week post-trial safety follow-up call, all serious adverse events, adverse events, and adverse reactions had resolved.

The mean number of injections given was distributed equally, with 24·7 (SD 1·4) in the semaglutide group, versus 24·2 (1·8) in the placebo group (appendix 2 p 10). In the semaglutide group, three participants reached a maximum tolerable once-weekly dose at 0·5 mg, two participants at 1·0 mg, five participants at 1·7 mg, and

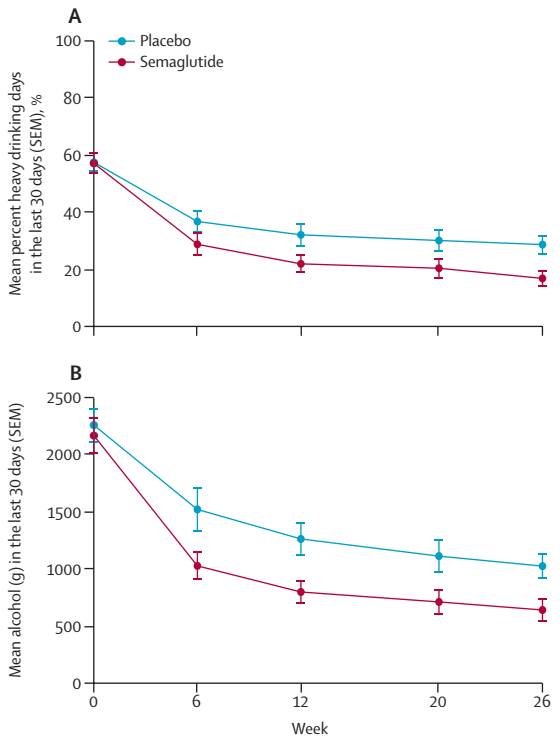

Figure 2: **Effects of once-weekly semaglutide compared with placebo on reduction in heavy drinking days and total alcohol consumption**
Changes from baseline (week 0) to follow-up (week 26) are shown for mean percent heavy drinking days in the last 30 days (A), and mean alcohol (g) consumed during the past 30 days (B), in participants randomly assigned to semaglutide 2·4 mg (n=54) or placebo (n=54). Participant level changes by treatment group are in appendix 2 (p 15). SEM=standard error of the mean.

the remaining participants at 2·4 mg. The placebo group completed the titration regimen corresponding to the 2·4 mg semaglutide dose. Analysis of the plasma semaglutide concentrations in patients without detectable plasma semaglutide at baseline showed 59·2 pmol/mL in the semaglutide group versus 0·00 pmol/mL in the placebo group (59·3 [95% CI 52·5 to 66·1; appendix 2 p 10), which is comparable to plasma semaglutide levels in other clinical trials.[19]

The number of therapy sessions received was similar in the two groups, with a mean of 6·8 (SD 2·3) sessions in the semaglutide group versus 6·6 (2·2) sessions in the placebo group (appendix 2 p 11).

Post-hoc analysis showed an effect size in the moderate range on heavy drinking days (Cohen's *d*=0·57 [95% CI 0·14–0·99]), total alcohol consumption (0·54 [0·11–0·96]), and number of drinks per drinking days (0·45 [0·02–0·88]). The number needed to treat for semaglutide according to the 2-level decrease in WHO risk drinking level was 4·3 (95% CI 2·33–30·3). Spearman's rank correlations indicated a significant association between heavy drinking days versus weight loss (ρ=–0·40, p=0·0038) in the semaglutide group (figure 3A), but not in the placebo group (ρ=0·03, p=0·85; figure 3B).

	Placebo (n=54)	Semaglutide (n=54)
Serious adverse events		
Admitted with abdominal pain*	0	1 (2%)
Hospitalised due to withdrawal symptoms	1 (2%)	0
Posterior vitreous detachment	1 (2%)	0
Hospitalised for acute coronary syndrome observation	1 (2%)	0
Adverse events and adverse reactions		
Nausea	4 (7%)	31 (57%)
Loss of appetite	8 (15%)	19 (35%)
Food aversion	1 (2%)	13 (24%)
Vomiting	1 (2%)	8 (15%)
Abdominal pain	4 (7%)	11 (20%)
Diarrhoea	11 (20%)	15 (28%)
Constipation	9 (17%)	19 (35%)
Reflux	1 (2%)	15 (28%)
Abdominal bloating	3 (6%)	2 (4%)
Increased belching	0	2 (4%)
Fatigue	10 (19%)	17 (32%)
Generalised itching	1 (2%)	3 (6%)
Headache	10 (19%)	11 (21%)
Dizziness	4 (7%)	7 (13%)
Injection site reaction	2 (4%)	1 (2%)
Outpatient detoxification	1 (2%)	0
Elevated plasma amylase†	0	4 (7%)
Elevated liver parameters‡ (AST, ALT, and GGT)	21 (39%)	15 (28%)
Sleep disturbances	2 (4%)	4 (7%)
Depression diagnosed in primary care	1 (2%)	0
Worsening of anxiety level	0	1 (2%)
Suicidal thoughts	1 (2%)	0
Fall (no hospitalisation)	2 (4%)	3 (6%)
Miscellaneous	21 (39%)	30 (56%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. GGT=γ-glutamyl transferase. *The only serious adverse event recorded in the semaglutide group was one hospital admission due to unspecific abdominal pain (semaglutide 0·25 mg), but this did not lead to trial discontinuation. †Reference range <105 U/L; highest observed level 123 U/L. ‡Total participants n=24; AST (n=8), highest observed level 125 U/L; ALT (n=12), highest observed level 121 U/L; GGT (n=16), highest observed level 209 U/L.

Table 3: **Serious adverse events, adverse events, and adverse reactions**

Discussion

To our knowledge, this is the first RCT to investigate the effects of the GLP-1 receptor agonist semaglutide in treatment-seeking patients with alcohol use disorder, and it showed significant effects on multiple alcohol-related and somatic outcomes, aligning with preclinical evidence and registry studies.[7]

Recent advances in pharmacotherapy have shifted focus from strict abstinence to harm reduction via reduced alcohol consumption, and WHO drinking risk levels are now accepted by the FDA as the primary endpoint in alcohol RCTs.[20] Our finding of a reduction in WHO risk drinking levels, and the 2-level reduction with semaglutide

compared with placebo (appendix 2 p 9), is aligned with this reductionist approach and with the drinking reduction goals of many patients.[20] This reduction in WHO risk drinking levels is associated with long-term reduction in alcohol-related negative consequences, improvement in mental health,[21] and aligns with the improvement of the self-evaluated general and psychological health in the present semaglutide group, although these improvements were modest (appendix 2 p 9).

Analysis of medication Cohen's *d* effect sizes indicated noteworthy findings, with estimates falling within the medium range for number of heavy drinking days, total alcohol consumption, and number of drinks per drinking day. The effect size estimates are clinically meaningful in the context of already established FDA-approved pharmacotherapies for alcohol use disorder, for which RCTs indicate that FDA-approved agents generally confer small to moderate effects in reducing heavy drinking episodes.[22,23] For acamprosate, a meta-analysis reported no significant reduction in heavy drinking days compared with placebo,[24] and for extended-release naltrexone, a meta-analysis showed a moderate effect, corresponding to approximately 1·2 fewer heavy drinking days per month relative to placebo.[25] In a recent review, the efficacy of several therapeutics for alcohol use disorder was evaluated with respect to the number needed to treat for a 2-level decrease in the WHO risk level endpoint.[20] On the basis of the present data (appendix 2 p 9), the number needed to treat for semaglutide is 4·3, indicating that semaglutide could be more efficacious than approved medications for alcohol use disorder, for which the number needed to treat is 7 or higher.[20]

The precise mechanisms of action of GLP-1 receptor agonists remain incompletely understood. Preclinical studies have reported that stimulation of brain GLP-1 receptors is a prerequisite for GLP-1 RA-induced reduction in alcohol consumption,[26] and in an earlier paper we have shown that treatment with the GLP-1 RA exenatide reduced alcohol cue-induced activation in reward-related brain areas in patients with alcohol use disorder.[12] These findings point towards a central mechanism of action. However, the precise molecular mechanism of action has not been elucidated; the prevailing hypothesis suggests that the therapeutic effects arise from overlapping neurobiological and peripheral mechanisms that modulate both metabolic regulation and reward-related pathways shared between obesity and alcohol use disorder.[27] In line with this, we observed a significant association between weight loss and reduced alcohol consumption.[27]

In this cohort, the mean weight loss was comparable to that of individuals with obesity, treated with semaglutide.[28] The Spearman's rank correlation indicates an association between heavy drinking days and weight loss in the semaglutide group, but not in the placebo group (figure 3). As caloric intake was not assessed, it is not possible to establish whether the observed effect of semaglutide on alcohol consumption was primarily attributable to the caloric content of alcohol. When evaluating changes in beverage preference (appendix 2 p 7), we observed a similar shift in self-reported preference patterns across the two groups, indicating no semaglutide-induced change in consumption patterns. As only three individuals in the semaglutide group had weight loss of less than 2·5 kg (appendix 2 p 13), it is not possible to conclude whether the potential effects are independent of weight loss. Semaglutide-induced gastrointestinal symptoms are mostly transient. Consequently, it is unlikely that adverse effects (eg, nausea) should account for the reduction in alcohol

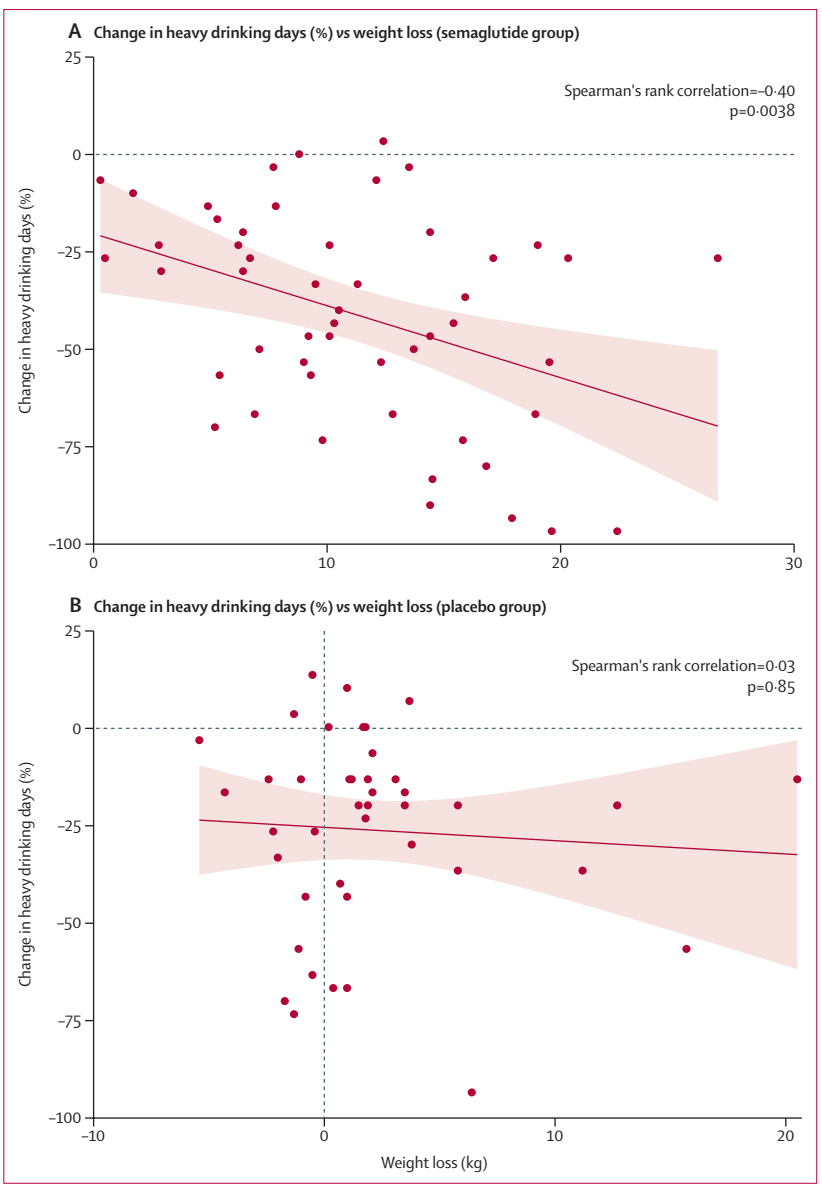

***Figure 3*: Change in heavy drinking days correlated with weight loss**
(A) Changes from baseline (week 0) to follow-up (week 26) are shown for heavy drinking days versus weight loss in the semaglutide group. (B) Changes from baseline (week 0) to follow-up (week 26) are shown for heavy drinking days versus weight loss in the placebo group.

consumption, as the effects of semaglutide continued throughout the study (figure 2).

Semaglutide reduced alcohol consumption on average, but a subset of participants showed little or no response, even at the highest dose of 2·4 mg once-weekly (appendix 2 p 15), paralleling the non-responder phenomenon observed in obesity studies[28] and highlighting the influence of individual phenotypes on treatment efficacy.[27] We found significant reductions within the subgroup of participants with severe alcohol use disorder and within the subset with 12–17 heavy drinking days at baseline (appendix 2 p 10). However, the number of participants differed considerably between the two DSM-5 alcohol use disorder symptom subgroups with 16 in the moderate subgroup and 92 in the severe subgroup (appendix 2 p 10). Low statistical power in the moderate symptom subgroup could partly explain why a significant effect of semaglutide was detected only in the severe symptom group. Moreover, the size of the four subgroups defined by the baseline number of heavy drinking days varied from 17 to 32 participants per subgroup, which might explain why the overall significant effect could not be detected in all subgroups despite consistent trends towards benefit (appendix 2 p 10). It should be stressed that differences in significance in each subgroup in itself do not reflect that the estimated treatment differences between two groups are necessarily different.

We found no effect of semaglutide on the FTND score or daily cigarette consumption, despite preclinical reports suggesting a potential effect.[29] The absence of effect might be attributable to the small cohort of smokers or the relatively low baseline severity of nicotine dependence. These findings are consistent with data from the exenatide alcohol study,[12] and results from RCTs in smokers, reporting mixed effects.[29]

GLP-1 receptor agonists are considered safe; however, safety data in individuals with alcohol use disorder remain scarce. On the one hand, weekly visits provided substantial oversight of safety, but CBT might have mitigated some adverse effects. On the other hand, the focus on and systematic inquiry into adverse effects might have contributed to a higher number of reported events. The gastrointestinal side-effects reported were not measured systematically (eg, with a visual analogue scale score), so no correlation with alcohol consumption can be done. The reported gastrointestinal side-effects were mostly transient and mild to moderate. When compared with other semaglutide RCTs, symptoms occurred slightly more frequently for all participants in this trial than in individuals with a comparable BMI but without alcohol use disorder.[28] These adverse events were also more frequent in the placebo group, suggesting that this population has an increased gastrointestinal vulnerability in general. In real-world settings without such intensive monitoring, the safety profile might differ. Nonetheless, our findings provide important insight into potential adverse effects under closely monitored conditions and underscore the need for further studies in routine clinical practice.

This trial has several limitations. The inclusion criterion of BMI of 30 kg/m² or higher limits the generalisability of the findings to the entire population of patients with alcohol use disorder. Approximately 890 million adults worldwide (~16%) have obesity (BMI ≥30).[30] The findings from this trial provide support for broadening the indication for semaglutide to alcohol use disorder in patients with a BMI of 30 kg/m² or higher, which could potentially benefit millions of individuals, given that an estimated 8 million adults in the USA alone have both obesity and high consumption of alcohol.[31] Such targeted approaches are consistent with the recognition of alcohol use disorder heterogeneity and the move towards precision medicine.[32]

In our trial, the administration pens required weekly visits for 26 weeks, for all participants, to receive the assigned treatment. To optimise retention, all participants were offered CBT, consistent with current recommendations for alcohol RCTs, in which investigational treatments are evaluated alongside effective interventions such as psychotherapy.[33] Although this design of CBT offering and weekly visits among all participants likely increased the placebo response, it also underscores that our findings show even more robust efficacy of semaglutide.

The overall dropout rate was comparable to that of other alcohol RCTs;[18] more participants in the placebo group discontinued than in the semaglutide group, and this pattern aligns with observations from other clinical obesity trials of semaglutide.[28] The primary reasons for dropout in the placebo group were the initiation of semaglutide treatment from external sources and a perceived lack of treatment effect. These findings underscore the risk of functional unblinding in incretin therapy trials as, in general, the absence of expected side-effects or weight loss in placebo recipients and their presence in active treatment recipients could compromise blinding and lead CBT providers to reinforce treatment effects inadvertently. However, in our trial, substantial heterogeneity in weight loss was observed, with some participants in the placebo group losing up to 25 kg (appendix 2 p 13), and some participants receiving semaglutide had little or no weight loss. Additionally, the high frequency of reported adverse events in the placebo group in this trial (table 3) further hampered the potential unblinding for both participants and study personnel.

A key limitation of this study is that no alcohol follow-up data were collected after week 26 and, therefore, alcohol consumption after trial termination could not be assessed. Future studies should include longer-term follow-up to evaluate the potential sustained effects of the treatment. Lastly, a limitation was the study population being predominantly White, limiting the generalisability to a broader population, so greater effort should be made for diverse inclusion in future trials.

In summary, the effects of semaglutide suggest that the treatment effect was sufficiently large to be detected despite the modest sample size, and self-reported alcohol consumption was validated with the gold-standard phosphatidyl ethanol biomarker, further enhancing the validity of our findings.

To our knowledge, this RCT is the first to show that once-weekly semaglutide reduces heavy drinking days and WHO drinking-risk levels in treatment-seeking patients with alcohol use disorder and comorbid obesity. This finding adds to the growing evidence for use of GLP-1 receptor agonists in alcohol use disorder, supporting an expanded indication for semaglutide, potentially affecting millions of individuals, given the global burden of alcohol use disorder and comorbid obesity. Importantly, key limitations and safety uncertainties do persist, and additional research is needed before off-label use can be endorsed.

Contributors

Conceptualisation: AF-J and MKK. Data curation: AJ, MKK. Statistical power analysis: AF-J, MKK, and CTE. Statistical analysis plan: MKK, AJ, AF-J, and CTE. Funding acquisition: MKK and AF-J. Clinical investigations: MKK, JNP, LR, and SKJ. Plasma phosphatidyl ethanol concentration analysis: MLB. Plasma semaglutide concentration measurements: JJH and BH. Methodology: MKK, AFJ, TV, HB, NDV, GFK, and GMK. MKK was a study physician and subinvestigator, AF-J was the principal investigator, and UBK was the institutional head of the department with responsibility for initiating and leading the clinical trial. Validation of clinical data: AF-J, AJ, MKK, and CTE. Preparation of figures: AJ, MKK, MEJ, and AF-J. Original manuscript drafting: MKK. All authors had access to the data, contributed to the review of the manuscript, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

MKK has served as a consultant for Phamacotherapies for Alcohol and Substance Use Disorders Alliance and Guidepoint. AFJ has received an unrestricted grant from Novo Nordisk to investigate the effects of semaglutide on metabolic disturbances in participants with schizophrenia treated with antipsychotics; serves on a RCT advisory panel for Novo Nordisk, receiving no honorarium; and has served as a consultant for Phamacotherapies for Alcohol and Substance Use Disorders Alliance and Guidepoint. TV has served on scientific advisory panels and been part of speakers bureaus for Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, Mundipharma, Novo Nordisk, Carmot/Roche, Sanofi, Sun Pharmaceuticals, and Zealand Pharma; and served as a consultant for Amgen, Astra-Zeneca, BMS, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, Mundipharma, Novo Nordisk, Carmot/Roche, Sanofi, Sun Pharmaceuticals, and Zealand Pharma. JJH has received a grant from the Novo Nordisk Foundation to the Center for Basic Metabolic Research at Copenhagen University (NNF23SA0084103); has given lectures and received travel support from AstraZeneca, Eli Lilly, and Decheng Capital Global Lifesciences Fund; has served as a consultant for Third Bridge, Metaphor Biotechnologies, Vial Health Technology, Crinetics Pharmaceuticals, Immunic Therapeutics, Guidepoint, Fractyl Health, Alcimed, Soffinova Partners, and Jefferies International; has received support for attending meetings and/or travel from the Endocrine Society and Eli Lilly; participates on an advisory board for Novo Nordisk; is a cofounder and board member of Antag Therapeutics and Bainan Biotech, and sits on the boards of both, unpaid; and has stock options with Antag Therapeutics. All other authors declare no competing interests.

Data sharing

All de-identified individual participant data, except brain imaging data and alcohol diaries, and the protocol and statistical analysis plan (appendix 1), are available in the Mendeley database from publication (DOI 10.17632/fr522rsvyp.1). The criteria for access to data are a methodologically sound proposal with an approved aim directed to the corresponding author via email. Data will be available for 5 years from publication.

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