



## OPEN Semaglutide and Tirzepatide reduce alcohol consumption in individuals with obesity

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Alcohol Use Disorder (AUD) contributes significantly to global mortality. GLP-1 (Glucagon-like peptide-1) and GLP-1/GIP (Glucose-dependent Insulinotropic Polypeptide) agonists, FDA-approved for managing type 2 diabetes and obesity, where the former has shown to effectively reduce the consumption of alcohol in animal models but no reports exist on the latter. In this report, we conducted two studies. In the first study, we conducted an analysis of abundant social media texts. Specifically, a machine-learning based attribution mapping of ~68,250 posts related to GLP-1 or GLP-1/GIP agonists on the Reddit platform. Secondly, we recruited participants (n = 153; current alcohol drinkers; BMI ≥ 30) who self-reported either taking Semaglutide (GLP-1 agonist), Tirzepatide (the GLP-1/GIP combination) for ≥ 30 days or, as a control group; no medication to manage diabetes or weight loss for a within and between subject remote study. In the social media study, we report 8 major themes including effects of medications (30%); diabetes (21%); and Weight loss and obesity (19%). Among the alcohol-related posts (n = 1580), 71% were identified as craving reduction, decreased desire to drink, and other negative effects. In the remote study, we observe a significantly lower self-reported intake of alcohol, drinks per drinking episode, binge drinking odds, Alcohol Use Disorders Identification Test (AUDIT) scores, and stimulating, and sedative effects in the Semaglutide or Tirzepatide group when compared to prior to starting medication timepoint (within-subjects) and the control group (between-subjects). In summary, we provide initial real-world evidence of reduced alcohol consumption in people with obesity taking Semaglutide or Tirzepatide medications, suggesting potential efficacy for treatment in AUD comorbid with obesity.

Alcohol Use Disorder (AUD) is a multi-faceted chronic relapsing brain disorder and contributes greatly to global mortality, yet it remains one of the most undertreated conditions. The only FDA-approved treatments (disulfiram, naltrexone, and acamprosate) have been modestly successful in treating AUD (e.g., naltrexone reduces relapse rates by 5%) (for a detailed review and meta-analysis<sup>1,2</sup>), but still are severely under-prescribed. Further, 2/3 of patients relapse within the first year in abstinence-based treatment models<sup>3</sup>. A meta-analysis reported that, at maximum, 50% of individuals diagnosed with AUD achieve remission during extended follow-up periods<sup>4</sup>. Therefore, a crucial need for novel and effective AUD treatments still remains.

Incretin hormones (such as Glucagon-like peptide; GLP-1 and glucose-dependent insulinotropic polypeptide; GIP), produced in the intestine and brain in response to nutrients in the gut, are responsible for maintaining glycemic control<sup>5</sup>. Shared neural mechanisms between the food reward system and AUD pathways are well established<sup>6–9</sup>. The ventral tegmental area (VTA) and nucleus accumbens (NAc), key brain areas involved in the reinforcing effects of food and alcohol abuse, contain GLP-1 receptors, indicating central mediation of GLP-1 agonists<sup>10</sup>.

GLP-1 peptides, FDA-approved for type-2 diabetes (e.g., Semaglutide and Exenatide) and weight loss (Semaglutide) have been studied for their effects on alcohol use in both preclinical and clinical studies (for a detailed review: 10). GLP-1/GIP peptide (Tirzepatide) has also been FDA-approved for treating type-2 diabetes. However, to our knowledge, there have been no research studies to investigate the effects of Tirzepatide on alcohol consumption. To date, only one clinical trial has investigated the effects of a GLP-1 agonist, exenatide, on individuals seeking treatment for AUD<sup>11</sup>. Although exenatide did not significantly reduce days of heavy drinking in the

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experimental group, fMRI revealed a significant attenuation of activity in the ventral striatum and septal area when images of alcohol were shown in the experimental group. Further analysis revealed a substantial reduction in heavy drinking in patients with obesity in the experimental group. To note, placebo effects in the group with BMI < 25 also showed a significant reduction in heavy drinking days. Additionally, there is strong preclinical evidence that GLP-1 agonists reduce alcohol intake in rats, mice, and vervet monkeys<sup>8,10,12–14</sup>. The administration of the GLP-1 agonist Exendin-4 (Ex-4) suppressed accumbal dopamine release in response to alcohol<sup>8</sup> and microinjection of Ex-4 to the nucleus accumbens or ventral tegmental area decreases alcohol intake, suggesting a possible central mechanism<sup>15–17</sup>. However, the administration of exendin-9–39, a GLP-1R antagonist, resulted in elevated alcohol consumption in rats<sup>7</sup>. Reduced alcohol intake, relapse-like drinking and attenuated alcohol-induced locomotor stimulation in mice and rats have been reported by administering semaglutide, one of the most commonly prescribed GLP-1 agonists<sup>12,18,19</sup>. Furthermore, other GLP-1 agonists, such as liraglutide<sup>20</sup>, dulaglutide<sup>21</sup>, and AC3174<sup>22</sup> have been shown to reduce alcohol-related behaviors. Although there is no literature on Tirzepatide, the strong mechanistic link between GIP and GLP-1 physiologically<sup>23</sup> warrants an investigation on alcohol use. Additionally, there is no evidence about the difference of GLP-1 effects on the severity of alcohol use. However, given the cumulative evidence in humans and animal models, the influence of GLP-1 agonists on alcohol-related behaviors cannot be denied.

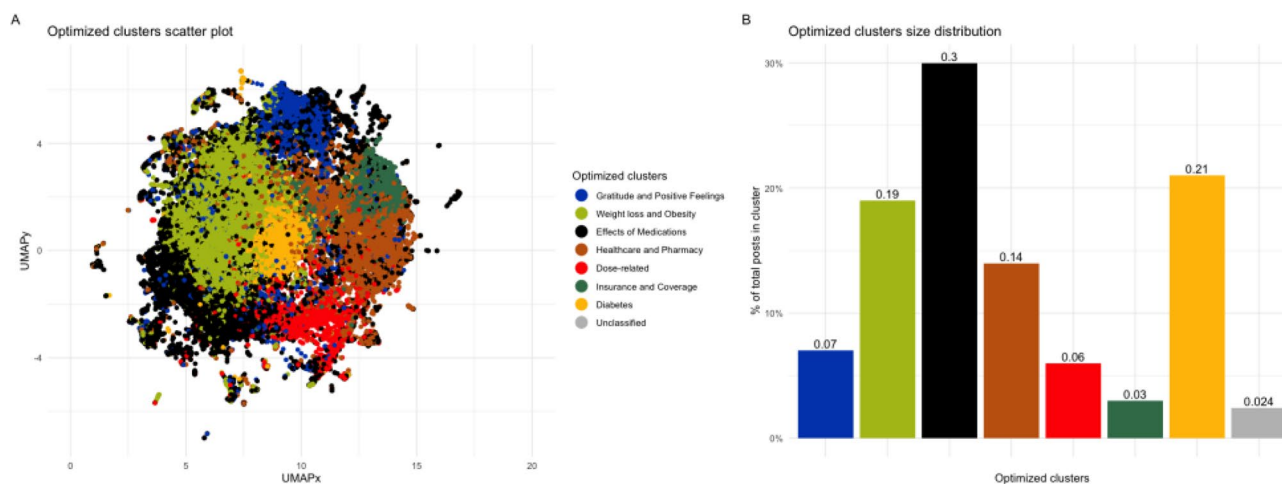
While administration of GLP-1 agonists has convincingly shown to reduce alcohol intake in preclinical models, more clinical data is crucial to understanding the efficacy and mechanism of several GLP-1 agonists and other related drug classes (e.g., Tirzepatide) on alcohol intake. In this article, we systematically analyzed social media discussions centered around GLP-1 agonists to generate insights and characterize the real-world evidence regarding effects on alcohol consumption in a substantial number of social media texts, replicating the workflow from<sup>24</sup> (Suppl. Fig. 1). Next, to gain detailed information on the impact of GLP-1 medication on alcohol consumption, we surveyed individuals with and without Semaglutide or Tirzepatide medications and assessed their historical and contemporary self-reports of alcohol usage and its direct effects. First, for the social media analysis, we retrieved all posts containing keywords related to GLP-1 agonists from Reddit, and categorized them by employing a machine learning algorithm to identify major themes of discussions. Next, we identified all alcohol-related posts and categorized them by impact on alcohol. Second, for the detailed reports on alcohol usage, we conducted a between and within participant remote survey among individuals taking Semaglutide or Tirzepatide or neither of these medications, who had a BMI greater than 30 and drank alcohol. Note heretofore, there have been no other reports of Tirzepatide effects on alcohol consumption. We hypothesize reduced alcohol intake and less impact of the self-reported effects of alcohol, in individuals on Semaglutide or Tirzepatide medications, as compared to those not taking these medications.

## Results

### Study 1: social media analysis

#### Optimum clusters identification

Using the two-step approach for cluster identification, 13 optimum clusters were identified by centroidal *k*-means clustering; as the trendline of the distortion score shows a steep fall before becoming linear-like at 13 (Suppl. Fig. 2). Figure 1A shows the 2-D visualization of the clusters using UMAP. Further inspection of the unigrams and bigrams of the top 50 keywords in each cluster revealed similar underlying themes, such as availability of medications in pharmacies and doctors' prescriptions were merged together in "Healthcare and Pharmacy". Therefore, we created 8 final clusters by merging similar clusters. Overall, 8 notable themes emerged from the discussions of GLP-1 related posts on reddit (Fig. 1B). Of these, discussions related to "Effects of Medications"



**Figure 1.** Final optimized clusters. Shown are the final optimized clusters obtained for our sample. (A) a scatterplot visualized by the UMAP model, we see the two UMAP components denoted as UMAPx and UMAPy represent the x and y axis of the scatter plot, with different colors to show the different clusters. (B) the distribution of posts into each of these clusters with corresponding colors.

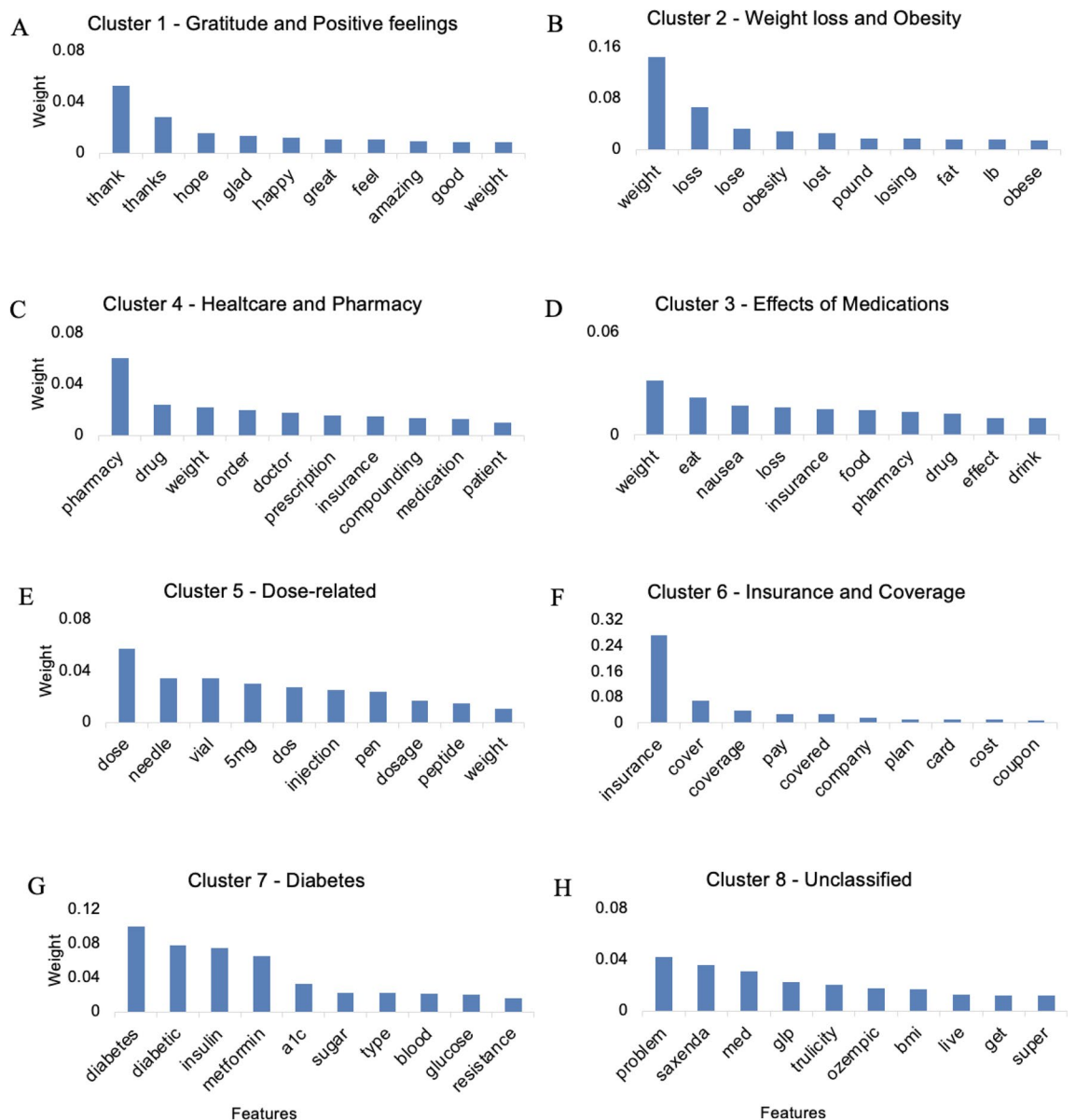
(30%), “Diabetes” (21%), “Weight loss and Obesity” (19%) and “Healthcare and Pharmacy” (14%) dominated (Fig. 1B).

*Important underlying features of optimized clusters*

A random forest based binary classifier was trained to obtain the underlying features and their respective weights. The results indicate unique underlying features for each theme; a) “thanks”, “hope” and “glad” are the most weighted features in Gratitude and Positive feelings, (Fig. 2A,B) “weight”, “lose” and “obesity” in Weight loss and Obesity, (Fig. 2B,C) “weight”, “eat”, “nausea” and “drink” are most notable in the effects of medications, (Fig. 2C,D) “pharmacy”, “drug”, and “doctor” in Healthcare and Pharmacy, (Fig. 2D,E) “dose”, “needle”, “vial” and “5 mg” in Dose-related discussions (Fig. 2E,F) “insurance”, “cover” in Insurance and Coverage, (Fig. 2F,G) “diabetes”, “diabetic”, “insulin” in Diabetes (Fig. 2G,H) “problem”, “med” in the Unclassified cluster (Fig. 2H). Overall, “weight”, “diabetes”, “pharmacy”, “dose” and “insurance” dominate the discussion among all identified themes.

*Data representation and exploration*

To further explore the discussions in the themes identified through the binary classifier, we visualized the top 30 unigrams; single words (Suppl. Fig. 3) and bigrams; two words (Suppl. Fig. 4) among our samples. The keywords in unigrams as well as bigrams disclosed that the identified themes broadly captured the related discussions; albeit with some overlap. For example, keywords such as weight, loss and weight loss were noted in all distinct



**Figure 2.** Underlying features obtained by training a supervised learning-based Random forest binary classifier. All clusters are identified by unique underlying features, as evident by the output (A–H).

clusters. Interestingly, effects of medications had discussions pertinent to suppression of appetite and reduced food cravings; with “don’t think”, “don’t want” and “food noise” observed as frequent keywords.

Case studies and news articles have pointed towards an unexpected side effect of GLP-1 medications, i.e. suppression of addictive behaviors such as reduction of food noise and loss of desire to consume alcohol<sup>25–28</sup>. To further investigate the effects of GLP-1 medications on alcohol consumption, we made word trees to visualize the discussions related to alcohol within each cluster. Alcohol-related discussions did not emerge as a distinct theme in our main analysis, but on inspection were found to be spread throughout the clusters. We performed a functional enrichment analysis to investigate if specific clusters overly represented alcohol posts. Most of the alcohol-related posts were over-enriched in two clusters: cluster 3; effects of medications (n = 826, p < 0.001), and cluster 2; weight loss and obesity (n = 439, p = 0.002). Usage of alcohol is represented by word trees in Cluster 2 and 3 (Figs. 3, 4, Suppl. Fig. 5); highlighted portions of text indicate posts related to the adverse effects or reduced usage of alcohol, e.g. I have zero desire to drink, alcohol consumption is way down, cravings are gone etc. 962 individuals made a total of 1580 alcohol related posts. Most notably, 71.7% (1134/1580) of the alcohol posts addressed reduced cravings, reduced usage and other negative effects due to drinking, containing keywords such as stopped, reduced, sick, full, nausea, don’t want, cutback, low tolerance, craving. On manual inspection of randomly selected alcohol-related posts, we confirmed that these were unique individuals posting about their own or closely-known experiences.

*Full order partial correlation analysis*

First, we calculated the proportions of posts on each time period in each cluster, organizing the data into a time series output. Full order partial correlation analysis on the time series output provided an insight into the strength of the relationship between the 8 identified optimum clusters (Fig. 5). We observed a majority of positive correlations among our clusters, indicating an uptick in concurrent discussions relevant to all themes e.g., gratitude and positive feelings have a significant positive correlation with all clusters, e.g., Insurance and coverage (R = 0.50, p < 0.001) and Diabetes (R = 0.29, p > 0.05) except Dose-related (R = - 0.19, p > 0.05). Most notable negative correlation was observed between effects of medication and Dose-related (R = - 0.06, p > 0.05) and Insurance and coverage (R = - 0.38, p < 0.05) discussions, indicating that there is a shift from discussing effects of medications to seeking information regarding doses and acquiring the medication through insurance, as the medication gains popularity.

**Study 2: remote study**

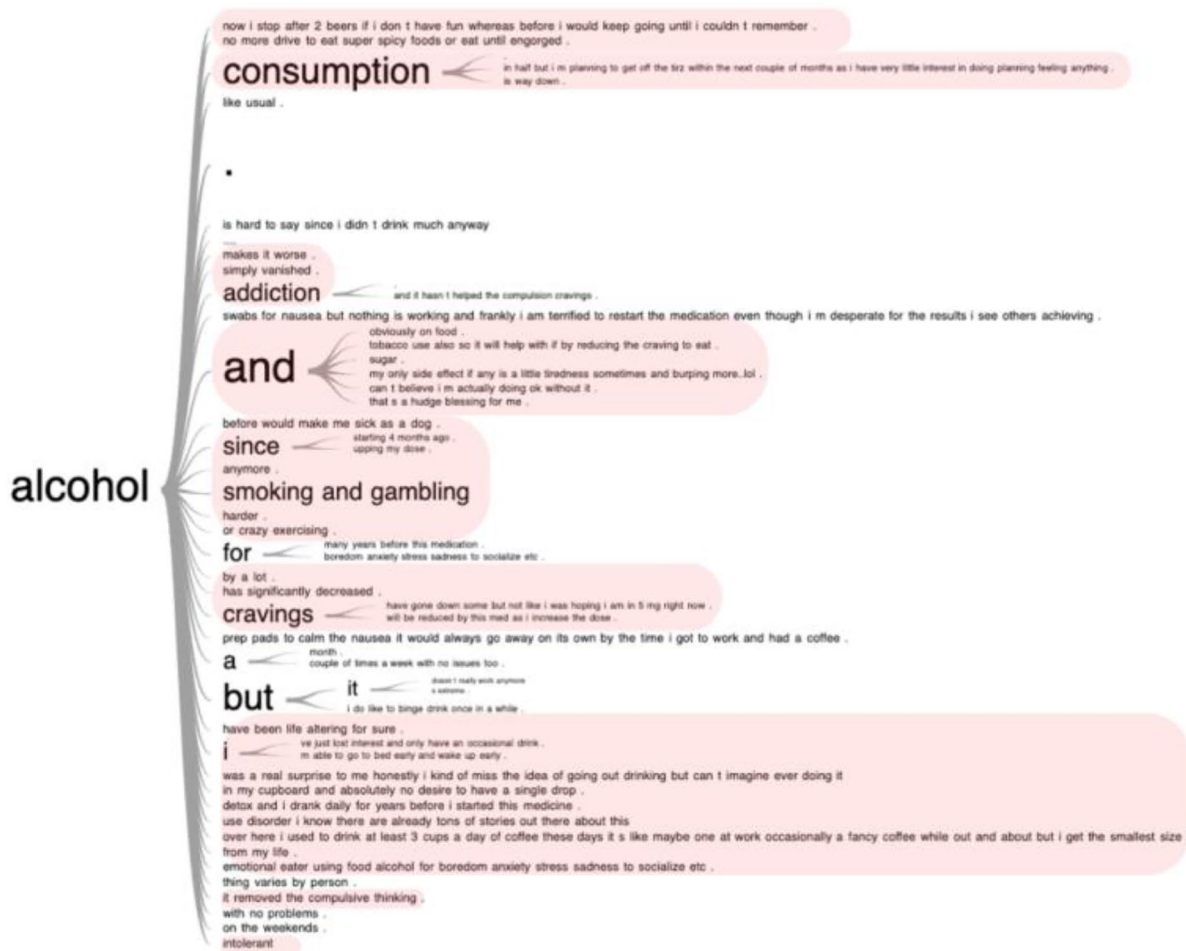
*Cohort characteristics*

We recruited 153 participants from various social media platforms to participate in our study. The demographics and cohort characteristics, none of which are significantly different between groups, are presented in Table 1.

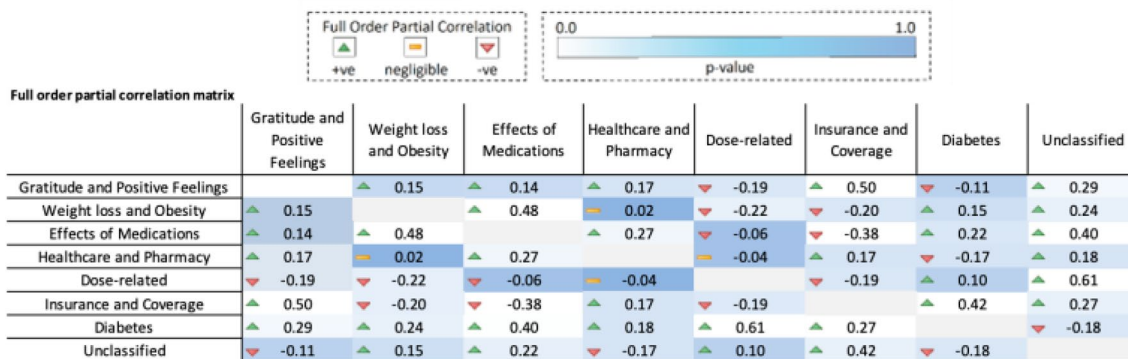


**Figure 3.** Alcohol related word tree. Prefixes from effects of medications cluster generated for the keyword “alcohol”. Any phrases related to a decrease/change in alcohol consumption or effects on alcohol are highlighted with red. It is evident that most alcohol-related posts point towards reduced alcohol usage.





**Figure 4.** Alcohol related word tree. Suffixes from effects of medications cluster generated for the keyword “alcohol”. Any phrases related to a decrease/change in alcohol consumption or effects on alcohol are highlighted with red. It is evident that most alcohol-related posts point towards reduced alcohol usage.



**Figure 5.** Optimum clusters full order partial correlation matrix with p values. Figure shows 8 unique GLP-1 post themes. Green arrows indicate a positive correlation between themes while a red arrow indicates a negative correlation between themes. The background color represents the p value, ranging from 0: white, to 1: dark blue.

Briefly, a majority of participants were white, female, ~ 40 years old, with an average education of ~ 15 years and a mean BMI around 35. Individuals on Tirzepatide (n = 50) reported a median dose of 7.5 mg [range 0.5–15 mg], and on Semaglutide variants: Ozempic or Wegovy (n = 54) reported a median dose of 1 [range 0.25–2.4] and Rybelsus (n = 2) reported doses of 7 mg and 14 mg. Individuals and their medication group and doses are reported in Table 1 and Suppl. Table 1 respectively.

	Control	Semaglutide	Tirzepatide	p-values
n	47	56	50	
Age [mean (SD)]	38.89 (11.29)	41.57 (9.08)	43.68 (8.22)	0.051
Education [mean (SD)]	15.39 (3.19)	15.00 (5.60)	15.40 (4.97)	0.887
Sex = male (%)	11 (23.4)	9 (16.1)	9 (18.0)	0.625
Ethnicity = not Hispanic or Latino (%)	42 (89.4)	53 (94.6)	48 (96.0)	0.377
Race (%)				0.395
Asian	0 (0.0)	0 (0.0)	1 (2.0)	
Black/African American	5 (10.6)	1 (1.8)	3 (6.0)	
Native Hawaiian or other Pacific islander	0 (0.0)	1 (1.8)	0 (0.0)	
Other	1 (2.1)	3 (5.5)	1 (2.0)	
White/Caucasian	41 (87.2)	50 (90.9)	45 (90.0)	
BMI [mean (SD)]	36.76 (6.69)	34.59 (5.69)	35.68 (6.80)	0.231
Medication (%)				–
Mounjaro (Tirzepatide)	–	–	50 (100.0)	
Ozempic or Wegovy (Semaglutide injection)	–	54 (96.4)	–	
Rybelsus (Semaglutide tablet)	–	2 (3.6)	–	
For weight loss (%)	–	51 (91.1)	36 (72.0)	–

**Table 1.** Cohort characteristics of participants (N = 153).

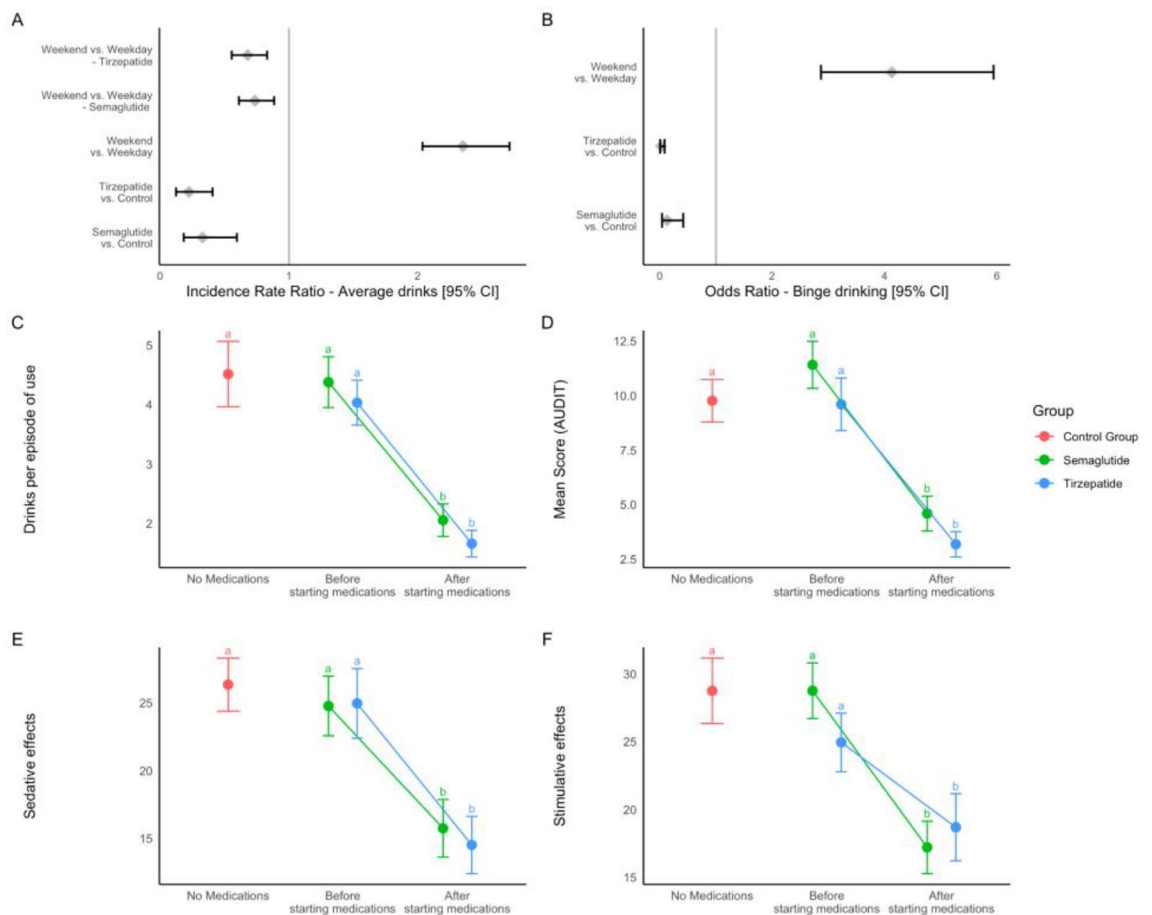
#### *Changes in alcohol consumption*

TLFB. We investigated between-subjects changes (control vs. medication groups) in alcohol consumption through the validated remote TLFB instrument. Participants drank significantly more on weekends than on weekdays ( $B = 0.85$ ,  $SE = 0.07$ ,  $p < 0.001$ ). Individuals with obesity on Semaglutide ( $B = -1.31$ ,  $SE = 0.30$ ,  $p < 0.001$ ) or Tirzepatide ( $B = -1.54$ ,  $SE = 0.31$ ,  $p < 0.001$ ) had on average significantly fewer drinks than their counterparts not on any medication for diabetes or weight loss. Additionally, we found a significant two-way (Time x Group) interaction term in the model with lowest BIC, suggesting reduced drinking both on weekdays and weekends in the Semaglutide ( $B = -0.17$ ,  $SE = 0.10$ ,  $p = 0.08$ ) and Tirzepatide ( $B = -0.45$ ,  $SE = 0.10$ ,  $p < 0.001$ ), when compared to control (Fig. 6A). Secondly, we used the drinks per day of an individual to make a binomial distribution of binge drinking; individuals were classified as 1 and 0 for binge drinking (drinks = 5+ and drinks = 4+ for males and females respectively<sup>29</sup>). In the optimal binomial model, there was a significant main effect of Time i.e., weekend vs. weekday ( $B = 1.4178$ ,  $SE = 0.1857$ ,  $p < 0.001$ ) and Group i.e., Semaglutide vs. Control ( $B = -2.0517$ ,  $SE = 0.6002$ ,  $p < 0.001$ ) and Tirzepatide vs. Control ( $B = -3.7920$ ,  $SE = 0.6764$ ,  $p < 0.001$ ; Fig. 6B), indicating that these medications reduce the odds of binge drinking. Overall, both average drinks and odds of binge drinking were found to be significantly lower in the medication groups i.e., Semaglutide and Tirzepatide, as compared to the control group.

AUDIT and drinks per episode of use. We report a main effect of Time ( $B = 6.63208$ ,  $SE = 0.76773$ ,  $p < 0.001$ ), prior to and while on medications, indicating that AUDIT scores decreased after the participants started their current dose of Semaglutide or Tirzepatide (Fig. 6D). Complementary to change in TLFB and AUDIT scores, drinks per episode of regular use was also significantly lower after the participants started their current dose of their medication ( $B = 2.3443$ ,  $SE = 0.2668$ ,  $p < 0.001$ ) (Fig. 6C). However, we did not find a dose-dependent change in average drinks or AUDIT scores in the medication groups, although a visual downward trend could be observed in the Tirzepatide group. (Suppl. Fig. 6). Finally, for the between group comparison, the current time point for both AUDIT (Semaglutide:  $B = -5.0820$ ,  $SE = 1.306$ ,  $p = 0.001$ , Tirzepatide:  $B = -6.6920$ ,  $SE = 1.331$ ,  $p < 0.001$ ) and frequency per episode of use (Semaglutide:  $B = -2.469$ ,  $SE = 0.540$ ,  $p < 0.001$ , Tirzepatide:  $B = -2.838$ ,  $SE = 0.552$ ,  $p < 0.001$ ) was significantly lower when compared to control group (Fig. 6C,D). In summary, we have strong converging evidence of reduced alcohol use in individuals taking Semaglutide or Tirzepatide.

#### *The effects of alcohol intoxication are mitigated*

We also investigated how the effects of alcohol differed in individuals with medication, prior to and while taking their Semaglutide or Tirzepatide medication. The repeated measures analysis revealed a significant main time effect i.e. prior to and while on the medications for both the stimulative ( $B = -9.057$ ,  $SE = 1.623$ ,  $p < 0.001$ ; Fig. 6E) and sedative effects ( $B = -9.689$ ,  $SE = 1.760$ ,  $p < 0.001$ ; Fig. 6F). Additionally, as a between-group analysis, we compared the control group to each medication group for both time points. The control group was significantly different than the current time point for both medications (Semaglutide:  $B = -10.29$ ,  $SE = 3.02$ ,  $p = 0.004$ , Tirzepatide:  $B = -11.445$ ,  $SE = 3.08$ ,  $p = 0.003$ ), but was not different when compared to prior to starting each medication (n.s.). In summary, our results suggest that the effects of alcohol intoxication, particularly the stimulative and sedative effects, are reduced while taking these medications.



**Figure 6.** The remote study provides strong converging evidence of reduced alcohol use. **(A)** Incidence Rate Ratio of Average drinks calculated from the past 30 days Timeline Follow Back, as calculated by the lme4 package using the poisson distribution. **(B)** Odds Ratio of binge drinking over the past 30 days (binomial distribution, 0; no binge, 1; binge) Males (> 5 drinks), Females (> 4 drinks). **(A, B)** Grey diamonds represent the estimated incidence rate or odds ratio and the error bars are 95% confidence intervals. Findings are significant, since the 95% CI do not encompass 1. Comparison of **(C)** average drinks per episode of use **(D)** AUDIT scores **(E)** Sedative effects and **(F)** Stimulative effects of alcohol within and between groups. A significant reduction is seen both within (Before and after starting medications) and between (control vs. medication) groups for all four measures. Solid circles represent mean and the error bars are standard error of means. Significantly different points are denoted by different letters.

## Discussion

Here, we report a novel analysis of GLP-1 agonist and drinking related posts made to the social media platform reddit. Case studies and media articles have hinted at unexpected side effects of GLP-1 agonist medications, i.e. the suppression of addictive behaviors and desire to consume alcohol. The machine learning based analysis here provides preliminary empirical support of these phenomena by classifying and quantifying these experiences. We further report a reduction in alcohol consumption in a cohort of people self-reporting alcohol use and taking Semaglutide or Tirzepatide compared to controls. Participants endorsing Semaglutide and Tirzepatide use reported fewer drinks as measured by the TLFB, fewer binge episodes, and lower AUDIT scores compared to controls and compared to before starting their medication. Participants also reported less stimulating and less sedative effects of alcohol than before starting their medication and when compared to controls.

In contrast to self-reported surveys, passive observation has higher accuracy in areas where self-reporting doesn't, such as recall area and social desirability bias<sup>30</sup>. By integrating both methodologies, we adopt a multi-faceted approach wherein the qualitative analysis corroborates the outcomes of our self-reported survey, thereby diminishing potential biases. In our case, we find that not only is there a self-reported decrease in alcohol use in individuals as evident by self-reports in our remote study but also a notable association of decrease in appetite of alcohol with individuals in the comprehensive qualitative social media analysis.

There are only 3 medications approved by the US Food and Drug Administration (FDA) to treat AUD: disulfiram, naltrexone, and acamprosate and they have poor compliance. Disulfiram acts by inducing nausea upon alcohol consumption, naltrexone is a mu-opioid receptor antagonist, therefore having broad action on the reward system, and the action of acamprosate is less well understood, but it is likely an allosteric modulator

of GABA<sub>A</sub> receptors. Semaglutide and Tirzepatide are both GLP-1 receptor agonists, with Tirzepatide having additional action on and a higher affinity for glucose-dependent insulinotropic polypeptide (GIP) receptors.

The mechanism by which GLP-1 agonists reduce alcohol intake in humans is currently unknown, though a recent RCT reported reduced alcohol cue reactivity in the nucleus accumbens (NAc), a key region associated with alcohol's rewarding properties, after treatment with the GLP-1 agonist Exenatide<sup>11</sup>. This is in accordance with preclinical studies demonstrating the ventral tegmental area and NAc as key areas mediating the effects of GLP-1 receptor agonists on alcohol intake<sup>10,18</sup>. Recent studies using fluorescently labeled semaglutide have demonstrated binding in the nucleus accumbens<sup>18</sup>. Furthermore, infusion of Exendin-4 in NAc has been shown to attenuate alcohol self-administration and related behaviors in mice and rats<sup>15,31</sup>.

While GLP-1 agonists have been shown to have central nervous system action, another possible mechanism is slowed gastric emptying<sup>32-34</sup>, which could increase fullness and reduce alcohol consumption. This could explain the prevalence of "nausea" and "appetite suppression" terms in our social media study (Cluster 3; Suppl. Figs. 3 and 4). Additionally, oxidation of alcohol to acetaldehyde can occur in the stomach<sup>35</sup>, potentially explaining the increase in negative effects of alcohol reported in the social media study. In contrast, intraduodenal ethanol rapidly increases blood alcohol levels<sup>36</sup>. Therefore, slowed gastric emptying from the stomach to the upper intestine (duodenum) observed after GLP-1 agonist administration could lead to increased levels of acetaldehyde and an altered or blunted rise in blood alcohol content (BAC). Altering the rising curve of a drug greatly decreases its subjective effects and abuse potential<sup>37</sup>. A decrease in the rewarding effects of alcohol could be driving the decrease in AUDIT scores and drinks per week observed in our remote study. Reduced BAC could also explain the decreased sedative and stimulating effects reported by the participants, here. However, some reports suggest that gastric emptying may return to baseline levels over time<sup>38</sup>. Further mechanistic studies are needed to test these hypotheses and explore potential mechanisms of action of GIP analogues, such as Tirzepatide tested here, for reducing alcohol intake.

### Limitations

The self-report nature of both our studies is subject to selection bias. People experiencing particular effects on alcohol intake, whether positive or negative, are more likely to post about them than those experiencing none. Similarly, participants may have found a decrease in alcohol intake very salient and remembered drinking more before starting their medication. However, given our effects with two classes of drugs as well as cross sectional, between subjects findings, the decrease in drinking observed here is unlikely due to reporting biases alone. Our sample was largely white and female, further studies in more diverse populations are needed to examine sex and race differences. Here, we recruited only participants with obesity in the remote study, limiting our results to this specific population. Future research should investigate the effects of GLP-1 and GLP-1/GIP agonists on alcohol consumption in different weight ranges and between different drug classes. We also report similar levels of alcohol reduction across medication doses (Suppl. Fig. 6), future studies examining optimal dose for alcohol reduction are needed.

### Conclusions

Here we provide a principled analysis of social media posts detailing a reduction in alcohol consumption while taking GLP-1 and Tirzepatide medication. In addition, we report a reduction in average number of drinks, binge drinking, AUDIT score, and the sedative/stimulating effects of alcohol in individuals taking Semaglutide or Tirzepatide in our remote study. These findings add to a growing literature detailing a reduction in alcohol intake after GLP-1 agonist medications. To our knowledge this is the first report of decreased alcohol consumption following Tirzepatide use. Further RCTs are needed to fully explore the therapeutic potential of GLP-1 agonists and GIP/GLP-1 combination drugs for the treatment of Alcohol Use Disorder.

### Methods

#### Study 1: social media analysis

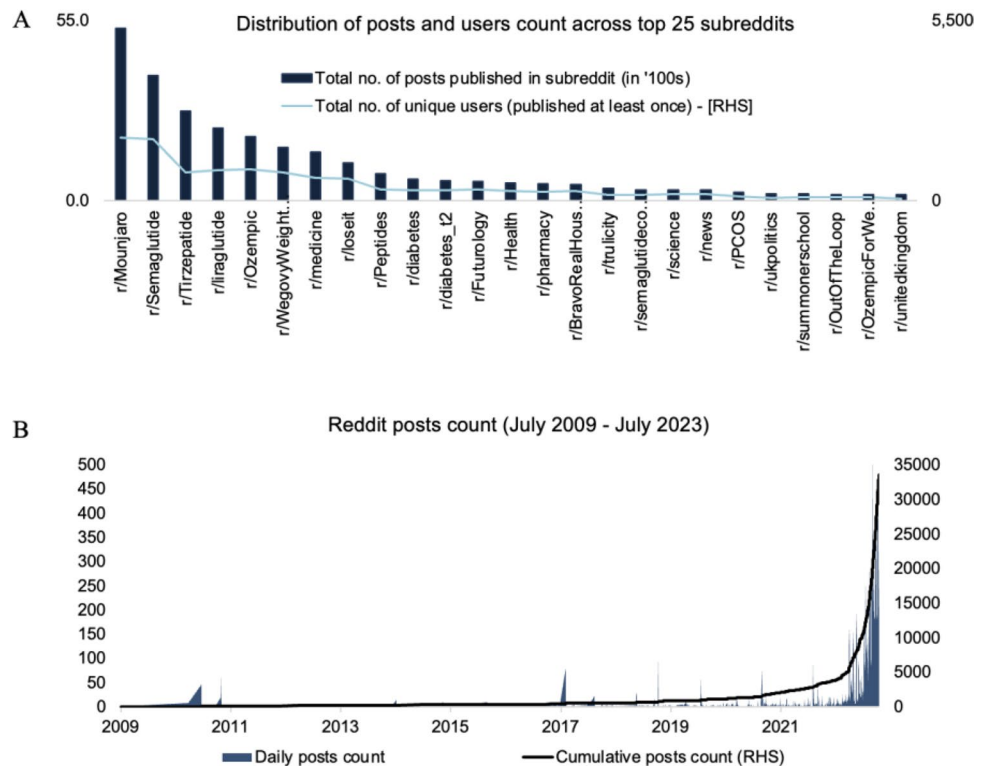
##### *Data collection*

Reddit posts and their comments were extracted using a list of keywords containing all GLP-1 approved medications (i.e., GLP-1, GIP, GLP1, dulaglutide, exenatide, byetta, semaglutide, liraglutide, lixisenatide, rybelsus, mounjaro, tirzepatide, wegovy, ozempic, trulicity) using the Reddit extractor tool available on Apify (apify.com). Reddit extractor tool allows to extract posts and comments using a set of keywords and export the data in multiple formats. 68,250 posts and comments from 2009 to 2023 were extracted from 313 subreddits. The top 25 subreddits contained 89% of the total extracted posts and comments (Fig. 7A), and discussions started to spike closer to 2021 (Fig. 7B).

##### *Data preprocessing*

The data preprocessing stage is necessary to ensure the dataset's uniformity and quality for further analysis. Our focus is to identify underlying themes; hence we performed data cleaning by removing punctuation, capitalization, urls, and special characters. Further, for uniformity, the title of the post and body was merged, as the main idea is often written in the title. Subsequently, the text is cleaned further by removing English stop words, punctuation, capitalization, special characters, and duplicate posts. Finally, we removed comments shorter than 100 characters to reduce noise and enhance content depth. Following these steps, the processed file contained 33,609 relevant posts from 14,595 unique users, which was used in subsequent steps.





**Figure 7.** Data exploration and finalization. (A) Distribution of posts and users across top 25 subreddits. (B) Time-series of daily post count and cumulative post count between 2009 and 2023. Overall, we observe a large influx of posts in recent years, with most posts coming from January 2022 to July 2023. These posts largely came from the top 25 subreddits (89% of total posts), notably from subreddits with a focus specifically on GLP-1 and Tirzepatide.

#### Feature selection

Preprocessed data was then encoded by the Universal Sentence Encoder (USE) 4, a pre-trained state-of-the-art encoder, by TensorFlow<sup>39</sup>. The encoder translates each post and comment into 512 high-dimension, feature vectors to be used later in the analysis. To establish identifiers, each encoding is given an ID from their respective Reddit post/comment.

#### Cluster classification using machine learning

To determine the optimum number of themes discussed, we employed K-means<sup>40</sup> as an unsupervised machine learning<sup>41</sup> algorithm using scikit-learn (<https://scikit-learn.org/stable/>) machine learning library. Feature vectors generated from the previous step were used as an input to train the model and cluster labels are generated as an output. Elbow plot, which identifies the optimum number of clusters based on distortion scores<sup>42</sup>, was visualized using scikit-yb library (<https://www.scikit-yb.org/en/latest/>) (Suppl. Fig. 2). 13 optimum clusters were reported from the K-means trained model. Further, we inspected the top 100 unigrams and top 50 bigrams within each cluster. Based on our inspection, we merged clusters based on thematic similarities, finalizing an optimum 8 clusters which encapsulated the majority of discussions.

As a second step, we trained a supervised machine learning model to determine important features and their weights in each cluster. In each iteration of training the Random Forest<sup>43</sup> based binary classifier, each cluster was separately set to 1, while the rest were labeled 0 to identify the most important features driving the discussions underlying that cluster.

#### Data exploration and visualization

In order to visualize our clusters, we use Uniform Manifold Approximation and Projection (UMAP)<sup>44</sup> which turns our 512 dimensioned embeddings data into a visualizable, two-dimensional representation. Organization within the UMAP graphs indicates that there is an underlying structure within the clusters. Next, we generate word clouds for the top 30 unigrams and bigrams to reveal visually underlying structure or relationships within the clusters. Finally, we ran a hypergeometric test<sup>45</sup> for enrichment analysis of alcohol-related posts in all clusters. Next, we inspected all alcohol related posts within clusters identified by the enrichment analysis, using word trees to evaluate the attitude and feelings of individuals on GLP-1 medications towards alcohol. As an additional validation step, we manually inspected 10% of the alcohol-related posts (10 out of every 100) to understand if these posts were mere speculations. Randomly selected posts made by 962 unique individuals pointed towards first-hand experiences related to alcohol as also evident by the word trees (Figs. 3 and 4).

### Full order partial correlation analysis

A full order partial correlation analysis<sup>46</sup> was carried out to understand the strength of relationship between clusters; as it has the ability to show a direct relationship between two clusters. To this end, we analyzed 28 combinations, iterating over one combination at a time accounting for 8 optimized clusters.

## Study 2: remote study

### Participants and procedures

Individuals were recruited from social media including Facebook, Instagram and Reddit across the United States using flyers and paid ads and completed a one-session web-based survey administered on Qualtrics. Inclusion criteria included being: (a) a current alcohol drinker; (b)  $\geq 21$  years old; (c) a BMI  $\geq 30$ ; and (d) (i) either reported taking their current dose for  $\geq 30$  days of Semaglutide/Tirzepatide or (ii) did not report taking these medications (as a control group) for diabetes or weight loss. Participants completed original and adapted forms of validated assessments (see Supplemental document). In the group with medications, adapted forms of validated assessments were used to investigate differences prior to and while on the current dose of their medication. However, the control group (i.e., individuals with obesity not on these medications to treat type-2 diabetes or weight loss) reported these assessments for the current time point only. The study was approved by VT IRB, and informed consent was obtained from all participants prior to their participation in the study. All methods were performed in accordance with the relevant guidelines. Compensation was provided through a lottery system where 1 randomly selected participant per 50 participants received a \$50 gift card.

### Study measures

**Demographics.** Demographic data, such as age, height and weight (to calculate BMI), gender, race, education and ethnicity were assessed by a demographics questionnaire.

**Alcohol frequency.** We assessed alcohol consumption through three distinct questionnaires; Timeline Follow Back (TLFB), Alcohol use disorder identification test (AUDIT), and a subjective open-ended question about drinks per episode of use reading “How many standard drinks (refer to the standard drink picture) do you typically have during one episode of use when drinking alcohol?”. Participants could see a visualization of what a standard drink constituted of, e.g., 12 fl oz of regular beer or 5 fl oz of table wine is equivalent to one standard drink, when completing each measure. (a) Timeline Follow Back (TLFB). Alcohol use was measured through Timeline Follow Back (TLFB). TLFB has undergone rigorous research and examination<sup>47</sup> and has high test–retest reliability<sup>48</sup>. All participants completed the TLFB for the past 30 days to assess drinking frequency. (b) Alcohol use disorder identification test (AUDIT). AUDIT<sup>49</sup> consists of a ten-item scale that is designed to measure alcohol consumption, alcohol drinking behavior and alcohol-related problems. Control group participants completed the original AUDIT questionnaire, and the participants on medications (i.e., Semaglutide or Tirzepatide) completed an adapted form asking about each question prior to and while on their medication. (c) a subjective question about alcohol per episode of typical use was also asked to assess alcohol frequency. Similar to AUDIT, only participants taking Semaglutide or Tirzepatide completed questions asking about prior to and while on their medication, while control group participants only answered about their current typical use.

**The biphasic alcohol effects scale (BAES).** BAES is a 14-item scale that gauges feelings and emotions post alcohol consumption<sup>50</sup>. Participants report stimulative and sedative feelings on a 0–10 scale, 0 being not at all, to 10 being extremely for those select emotions. An example of some of the emotions are; difficulty concentrating, down, elated, energized and excited etc. For the medication group (i.e., those on Semaglutide or Tirzepatide), an adapted version of BAES was utilized to evaluate differences prior to and while on these medications.

## Statistical analysis

All statistical analyses were conducted using R software (version 4.2.2; R Core Team, 2022). An a priori sample size calculation was performed using repeated measures, within factor ANOVA. Using two groups (i.e., Semaglutide and Tirzepatide), two measurements (pre/post), a medium effect size (Cohen's  $f = 0.25$ ), alpha of 0.01, and 95% power, we required 76 participants. We extrapolated an equal proportion of control participants to bring the total number of participants required to complete the study to 114. We over-recruited due to unknown levels of data quality. Participant characteristics were described using mean (standard deviation) and frequencies, and compared between groups using a t-test and Chi-square test where appropriate. For each of our outcomes of interest, a repeated measure within-between interaction was performed with a group, time (i.e., pre/post), and group by time interaction as the explanatory variables and a random effect for the individual was performed using the lme4 package<sup>51</sup>. The outcome measures of interest include average drinks (Poisson distribution) and binge drinking (Binomial distribution) calculated from TLFB, AUDIT scores (Gaussian distribution), alcohol use per episode of use (Gaussian distribution) and the sedative and stimulative scores from the BAES scale (Gaussian distribution). For each outcome variable, the optimal model was considered to be the model with the lowest Bayesian Information Criterion (BIC). Results from our models are reported as odds ratios (Binomial), incidence rate ratios (Poisson) with 95% confidence intervals, and parameter estimates (Gaussian) with standard error of the means. Significance level was defined as  $p < 0.05$  for all analysis.

## Data availability

The raw data and code is available from the corresponding author (wkbickel@vtc.vt.edu) on reasonable request.

## Code availability

The raw data cannot be shared publicly as per Reddit policy, and is available from the corresponding author (wkbickel@vtc.vt.edu) on reasonable request. The code used to produce the results is made available in a public repository. <https://github.com/fatimaquddos/GLP1>.

Received: 18 September 2023; Accepted: 24 November 2023

Published online: 28 November 2023

## References

- Kranzler, H. R. & Soyka, M. Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA* **320**, 815–824 (2018).
- Jonas, D. E. *et al.* Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis. *JAMA* **311**, 1889–1900 (2014).
- Schuckit, M. A. Alcohol-use disorders. *Lancet* **373**, 492–501 (2009).
- Fleury, M.-J. *et al.* Remission from substance use disorders: A systematic review and meta-analysis. *Drug Alcohol Depend.* **168**, 293–306 (2016).
- Holst, J. J. The physiology of glucagon-like peptide 1. *Physiol. Rev.* **87**, 1409–1439 (2007).
- Davis, J. F. *et al.* Gastric bypass surgery attenuates ethanol consumption in ethanol-preferring rats. *Biol. Psychiatry* **72**, 354–360 (2012).
- Shirazi, R. H., Dickson, S. L. & Skibicka, K. P. Gut peptide GLP-1 and its analogue, Exendin-4, decrease alcohol intake and reward. *PLoS ONE* **8**, e61965 (2013).
- Egecioglu, E. *et al.* The glucagon-like peptide 1 analogue Exendin-4 attenuates alcohol mediated behaviors in rodents. *Psychoneuroendocrinology* **38**, 1259–1270 (2013).
- Blumenthal, D. M. & Gold, M. S. Neurobiology of food addiction. *Curr. Opin. Clin. Nutr. Metab. Care* **13**, 359–365 (2010).
- Dickson, S. L. *et al.* The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: A new role for mesolimbic GLP-1 receptors. *J. Neurosci.* **32**, 4812–4820 (2012).
- Klausen, M. K. *et al.* Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. *JCI Insight* **7**, 19 (2022).
- Chuong, V. *et al.* The glucagon-like peptide-1 (GLP-1) analogue semaglutide reduces alcohol drinking and modulates central GABA neurotransmission. *JCI Insight* **8**, 12 (2023).
- Thomsen, M. *et al.* Effects of glucagon-like peptide 1 analogs on alcohol intake in alcohol-preferring vervet monkeys. *Psychopharmacology* **236**, 603–611 (2019).
- Thomsen, M. *et al.* The glucagon-like peptide 1 receptor agonist Exendin-4 decreases relapse-like drinking in socially housed mice. *Pharmacol. Biochem. Behav.* **160**, 14–20 (2017).
- Vallöf, D., Kalafateli, A. L. & Jerlhag, E. Brain region specific glucagon-like peptide-1 receptors regulate alcohol-induced behaviors in rodents. *Psychoneuroendocrinology* **103**, 284–295 (2019).
- Abtahi, S., Howell, E. & Currie, P. J. Accumbal ghrelin and glucagon-like peptide 1 signaling in alcohol reward in female rats. *Neuroreport* **29**, 1046–1053 (2018).
- Colvin, K. J. *et al.* Differential effects of intra-ventral tegmental area ghrelin and glucagon-like peptide-1 on the stimulatory action of D-amphetamine and cocaine-induced ethanol intake in male Sprague Dawley rats. *Behav. Brain Res.* **421**, 113726 (2022).
- Aranäs, C. *et al.* Semaglutide reduces alcohol intake and relapse-like drinking in male and female rats. *EBioMedicine* **93**, 104642 (2023).
- Marty, V. N. *et al.* Long-acting glucagon-like peptide-1 receptor agonists suppress voluntary alcohol intake in male wistar rats. *Front. Neurosci.* **14**, 599646 (2020).
- Vallöf, D. *et al.* The glucagon-like peptide 1 receptor agonist liraglutide attenuates the reinforcing properties of alcohol in rodents. *Addict. Biol.* **21**, 422–437 (2016).
- Vallöf, D., Kalafateli, A. L. & Jerlhag, E. Long-term treatment with a glucagon-like peptide-1 receptor agonist reduces ethanol intake in male and female rats. *Transl. Psychiatry* **10**, 238 (2020).
- Suchankova, P. *et al.* The glucagon-like peptide-1 receptor as a potential treatment target in alcohol use disorder: Evidence from human genetic association studies and a mouse model of alcohol dependence. *Transl. Psychiatry* **5**, e583–e583 (2015).
- Seino, Y., Fukushima, M. & Yabe, D. GIP and GLP-1, the two incretin hormones: Similarities and differences. *J. Diabetes Investig.* **1**, 8–23 (2010).
- Kaushal, A., Acharjee, A. & Mandal, A. Machine learning based attribution mapping of climate related discussions on social media. *Sci. Rep.* **12**, 19033 (2022).
- Doucleff, M. Ozempic seems to curb cravings for alcohol. Here's what scientists think is going on. *NPR* (2023).
- Blum, D. Some people on ozempic lose the desire to drink. Scientists are asking why. *The New York Times* (2023).
- Moniuszko, S. Can Ozempic, Wegovy reduce alcohol, nicotine and other cravings? Doctor weighs in on what to know. *CBS News* <https://www.cbsnews.com/news/ozempic-wegovy-reduce-alcohol-nicotine-cravings-addiction/> (2023).
- Freeborn, J. Semaglutide and alcohol: Could a diabetes drug reduce drinking? <https://www.medicalnewstoday.com/articles/could-the-diabetes-drug-semaglutide-also-help-reduce-alcohol-use> (2023).
- Understanding Binge Drinking. <https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/binge-drinking>.
- Konitzer, T. *et al.* Comparing estimates of news consumption from survey and passively collected behavioral data. *Public Opin. Q.* **85**, 347–370 (2021).
- Allingbjerg, M.-L., Hansen, S. N., Secher, A. & Thomsen, M. Glucagon-like peptide-1 receptors in nucleus accumbens, ventral hippocampus, and lateral septum reduce alcohol reinforcement in mice. *Exp. Clin. Psychopharmacol.* **31**, 612–620 (2023).
- Edwards, C. M. *et al.* Exendin-4 reduces fasting and postprandial glucose and decreases energy intake in healthy volunteers. *Am. J. Physiol. Endocrinol. Metab.* **281**, E155–E161 (2001).
- Little, T. J. *et al.* Effects of intravenous glucagon-like peptide-1 on gastric emptying and intragastric distribution in healthy subjects: Relationships with postprandial glycemic and insulinemic responses. *J. Clin. Endocrinol. Metab.* **91**, 1916–1923 (2006).
- Dahl, K. *et al.* Oral semaglutide improves postprandial glucose and lipid metabolism, and delays gastric emptying, in subjects with type 2 diabetes. *Diabetes Obes. Metab.* **23**, 1594–1603 (2021).
- Yin, S. J. *et al.* Human stomach alcohol and aldehyde dehydrogenases: Comparison of expression pattern and activities in alimentary tract. *Gastroenterology* **112**, 766–775 (1997).
- Baraona, E. Site and quantitative importance of alcohol first-pass metabolism. *Alcohol. Clin. Exp. Res.* **24**, 405–406 (2000).
- de Wit, H., Bodker, B. & Ambre, J. Rate of increase of plasma drug level influences subjective response in humans. *Psychopharmacology* **107**, 352–358 (1992).
- Friedrichsen, M., Breitschaft, A., Tadayon, S., Wizert, A. & Skovgaard, D. The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. *Diabetes Obes. Metab.* **23**, 754–762 (2021).
- Cer, D. *et al.* Universal Sentence Encoder. arXiv [cs.CL] (2018).

40. Ikotun, A. M., Ezugwu, A. E., Abualigah, L., Abuhaija, B. & Heming, J. K-means clustering algorithms: A comprehensive review, variants analysis, and advances in the era of big data. *Inf. Sci.* **622**, 178–210 (2023).
41. Gentleman, R. & Carey, V. J. Unsupervised machine learning. In *Bioconductor Case Studies* (eds Hahne, F. et al.) 137–157 (Springer, 2008).
42. Syakur, M. A., Khotimah, B. K., Rochman, E. M. S. & Satoto, B. D. Integration K-means clustering method and elbow method for identification of the best customer profile cluster. *IOP Conf. Ser. Mater. Sci. Eng.* **336**, 012017 (2018).
43. Breiman, L. Random forests. *Mach. Learn.* **45**, 5–32 (2001).
44. McInnes, L., Healy, J. & Melville, J. *UMAP: Uniform Manifold Approximation and Projection for Dimension Reduction*. arXiv [stat.ML] (2018).
45. Hypergeometric function: RDocumentation. <https://www.rdocumentation.org/packages/stats/versions/3.6.2/topics/Hypergeometric>.
46. Opgen-Rhein, R. & Strimmer, K. From correlation to causation networks: A simple approximate learning algorithm and its application to high-dimensional plant gene expression data. *BMC Syst. Biol.* **1**, 37 (2007).
47. Sobell, L. C. & Sobell, M. B. Alcohol consumption measures. *Assess. Alcohol Probl.* **2**, 75–99 (1995).
48. Sobell, M. B., Sobell, L. C., Klajner, F., Pavan, D. & Basian, E. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. *Addict. Behav.* **11**, 149–161 (1986).
49. Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R. & Grant, M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction* **88**, 791–804 (1993).
50. Martin, C. S., Earleywine, M., Musty, R. E., Perrine, M. W. & Swift, R. M. Development and validation of the biphasic alcohol effects scale. *Alcohol. Clin. Exp. Res.* **17**, 140–146 (1993).
51. Bates, D., Mächler, M., Bolker, B. & Walker, S. Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* **67**, 1–48 (2015).

### Author contributions

W.K.B., F.Q., K.G., A.K.: Conceptualization and design of study. F.Q., Z.H., A.T.: Data Analysis. F.Q., Z.H., D.S., E.M.: Wrote the main manuscript text. A.T., A.D., K.G., W.K.B.: Supervision, Reviewing and editing the manuscript. F.Q., E.M., K.G., A.K.: Recruitment, Administrative and IRB submission.

### Funding

Funding was provided by Fralin Biomedical Research Institute at Virginia Tech Carillion.

### Competing interests

Although the following activities/relationships do not create a conflict of interest pertaining to this manuscript, in the interest of full disclosure, Dr. Bickel would like to report the following: W. K. Bickel is a principal of Health-Sim, LLC; BEAM Diagnostics, Inc.; and Red 5 Group, LLC. In addition, he serves on the scientific advisory board for Ria Health; and serves as a consultant for Lumanity. All other authors declare no potential conflict of interest.

### Additional information

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1038/s41598-023-48267-2>.

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