

Short communication

Comparing the effectiveness of a brief intervention to reduce unhealthy alcohol use among adult primary care patients with and without depression: A machine learning approach with augmented inverse probability weighting

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ABSTRACT

Background: The combination of unhealthy alcohol use and depression is associated with adverse outcomes including higher rates of alcohol use disorder and poorer depression course. Therefore, addressing alcohol use among individuals with depression may have a substantial public health impact. We compared the effectiveness of a brief intervention (BI) for unhealthy alcohol use among patients with and without depression.

Method: This observational study included 312,056 adult primary care patients at Kaiser Permanente Northern California who screened positive for unhealthy drinking between 2014 and 2017. Approximately half (48%) received a BI for alcohol use and 9% had depression. We examined 12-month changes in heavy drinking days in the previous three months, drinking days per week, drinks per drinking day, and drinks per week. Machine learning was used to estimate BI propensity, follow-up participation, and alcohol outcomes for an augmented inverse probability weighting (AIPW) estimator of the average treatment (BI) effect. This approach does not depend on the strong parametric assumptions of traditional logistic regression, making it more robust to model misspecification.

Results: BI had a significant effect on each alcohol use outcome in the non-depressed subgroup (−0.41 to −0.05, all p s < .003), but not in the depressed subgroup (−0.33 to −0.01, all p s > .28). However, differences between subgroups were nonsignificant (0.00 to 0.11, all p s > .44).

Conclusion: On average, BI is an effective approach to reducing unhealthy drinking, but more research is necessary to understand its impact on patients with depression. AIPW with machine learning provides a robust method for comparing intervention effectiveness across subgroups.

1. Introduction

Unhealthy alcohol use is the most globally prevalent substance use problem (Degenhardt et al., 2018). Epidemiological research and meta-analyses provide evidence of a strong link between unhealthy drinking and depression: the presence of one is associated with an increased risk of the other (Boden and Fergusson, 2011; Grant et al., 2015; Lai et al., 2015; Sullivan et al., 2005). Compared to either problem on its own, the co-occurrence of unhealthy drinking and depression is

associated with more severe alcohol use disorders (AUD), poorer course of depression, higher risk of suicide attempt, poorer global functioning, and lower quality of life and satisfaction (Brière et al., 2014; Levola et al., 2014; Sullivan et al., 2005). Unhealthy drinking patterns that do not meet criteria for an AUD are also highly prevalent among individuals with and without depression (Sullivan et al., 2005), who may be unaware that alcohol use is associated with adverse health consequences (National Institute on Alcohol Abuse and Alcoholism, 2005, updated 2007). Moreover, when patients with depression reduce unhealthy

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alcohol use, mental health symptoms often improve (Bahorik, 2016). Therefore, targeting unhealthy alcohol use can have public health impact in general, and on individuals with depression in particular.

In adult primary care, alcohol screening, brief intervention, and referral to treatment (SBIRT) is a population health approach that begins with routine alcohol screening to assess for unhealthy drinking, followed by brief intervention (BI) and/or referral to specialty treatment as needed (Babor et al., 2007). The most recent meta-analysis of randomized clinical trials (69 RCTs, 33,642 participants) found moderate-quality evidence in support of BIs for unhealthy alcohol use (Kaner et al., 2018). Despite these promising findings from RCTs, there is a paucity of effectiveness research of BI implemented in “real world” settings. An evaluation of SBIRT implementation at the United States Veterans Health Administration (30 facilities, 6210 participants with follow-up) did not find an association between BI and reduced rates of unhealthy drinking using multilevel logistic regression (Williams et al., 2014). Recently, we found small but significant effects of BI implemented in primary care of a large healthcare system (59 facilities, 312,056 participants) using marginal structural modeling, a method that accounts for potential biases arising from non-randomization of BI delivery and loss of follow-up by incorporating inverse probability weights (IPW) estimated with logistic regression (Chi et al., 2022). However,

there is insufficient and inconsistent evidence on the effectiveness of alcohol BI in patients with co-occurring depression (Boniface et al., 2017). For example, online (Montag et al., 2015) and face-to-face or telephone (Satre et al., 2013) BI led to significant improvement in drinking outcomes among patients with co-occurring depression. However, in studies with general practice patients (Grothues et al., 2008) and college students (Geisner et al., 2015), BI was less effective among participants with co-occurring depression.

Here our aim is to compare the effect of BI between depressed and non-depressed patients. We selected an augmented inverse probability weight (AIPW) approach with machine learning for several reasons. This approach, which can leverage data-adaptive machine learning algorithms to model complex nonlinear interactions, does not require parametric assumptions of traditional logistic regression that may not be realistic, such as the assumption of linear associations between covariates and outcomes (Kurz, 2022). AIPW is also doubly robust (i.e., reliable so long as either the treatment propensity or outcome model is correctly specified), which can reduce bias in estimates arising from misspecification of traditional logistic regression with or without IPW (Glynn and Quinn, 2010; Kurz, 2021, 2022).

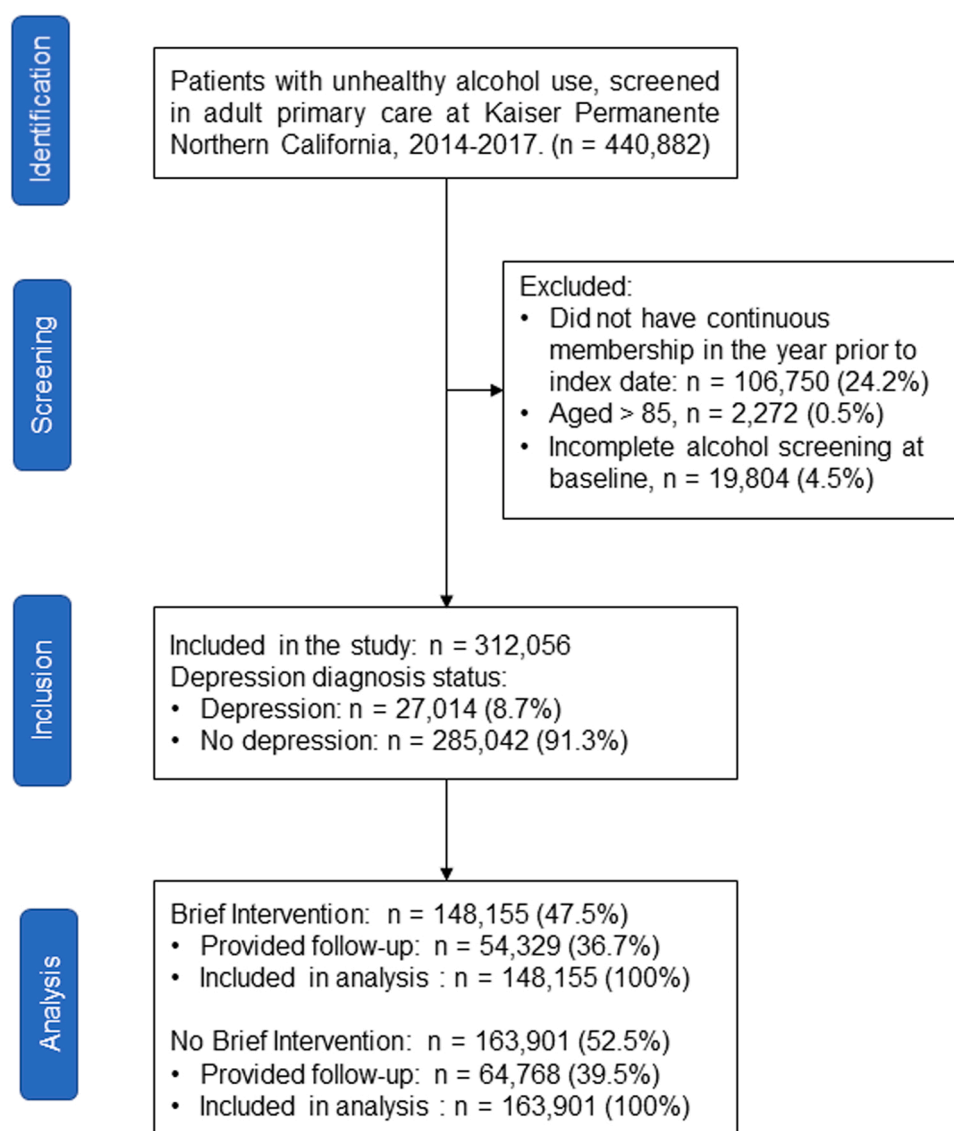


Fig. 1. STROBE Diagram of the study cohort.

2. Material and methods

2.1. Study design and cohort

Electronic health record (EHR) data were used to identify 440,882 patients who endorsed unhealthy drinking in Kaiser Permanente Northern California (KPNC) adult primary care between January 1, 2014, and December 31, 2017. For each patient, the index date was defined as the first positive screen for unhealthy drinking within the study window. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Diagram (Vandenbroucke et al., 2007) provided in Fig. 1 shows the exclusion criteria applied to define the cohort for this analysis, which consisted of 312,056 patients. Among them, 27,014 (8.7%) had an International Classification of Diseases (ICD) 9/10 diagnosis of depression. This study was approved by the Institutional Review Board at KPNC. Since this data-only study used existing protected health information in the EHR, waiver of informed consent was not required as data analysis is regulated by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.

2.2. Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT)

KPNC conducts systematic SBIRT in adult primary care (Palzes et al., 2020). Medical assistants use National Institute on Alcohol Abuse and Alcoholism (NIAAA) screening tools embedded in the EHR to assess alcohol use. If a patient meets criteria for unhealthy drinking, defined as exceeding the NIAAA recommended daily limits (>3 drinks/day for women and men aged ≥ 66 , or >4 drinks/day for men aged 18–65) and/or weekly limits (>7 drinks/week for women and men aged ≥ 66 , or >14 drinks/week for men aged 18–65), physicians are trained to conduct a BI using Motivational Interviewing principles (Miller and Rollnick, 2012). Additionally, physicians can provide referral to specialty Addiction Medicine treatment programs within KPNC. The EHR codes used to determine delivery of BI are provided in the [Supplementary Material](#).

2.3. Outcomes

Four 12-month outcomes were examined, defined as changes in: 1) heavy drinking days in the past 3 months, 2) drinking days per week, 3) drinks per drinking day, and 4) drinks per week. These outcomes are based on participant self-report. When a participant did not complete a 12-month screening, the previous screening was used (no less than 7 months post-index).

2.4. Baseline covariates

In a clinical trial, randomization is used to ensure that baseline differences between individuals that did and did not receive the intervention under evaluation occurred by chance. Effectiveness studies using observational data to estimate intervention effects must deal with potential confounds arising from nonrandomized intervention (Lu, 2009; Rosenbaum, 2002; Rubin, 1974). Non-random loss to follow-up may also introduce bias that can be mitigated by modeling the follow-up attrition process (Curtis et al., 2007). Additionally, both RCTs and observational studies can improve estimation of intervention effects by including covariates related to the outcome and must use appropriate methods to include patients with missing outcome data, since follow-up participation may be related to baseline characteristics, the type of intervention received, and their interactions (Rubin and Thomas, 2000). Accordingly, we selected a broad range of covariates hypothesized to be associated with intervention delivery, follow-up participation, and outcome.

Covariates were a total of 25 patient, provider, and facility characteristics. Patient characteristics were sex, age, race/ethnicity, insurance

type categorized as either commercial, Medicaid, Medicare, or other/unknown, smoking status, physical activity, body mass index, Charlson comorbidity score (Charlson et al., 2008), presence of alcohol, drug, or other mental health disorders, neighborhood deprivation index from geocoded census data (Messer et al., 2006), and healthcare services utilization. Baseline alcohol consumption was defined as exceeding daily limit, weekly limit, or both daily and weekly limits (per NIAAA guidelines). Provider characteristics were age, sex, race/ethnicity, specialty (Internal Medicine, Family Practice, Other) and years of service. The year of screening, index facility, and department were also recorded.

2.5. Analyses

To estimate BI effects, we used augmented inverse probability weighting (AIPW) which incorporates estimates of intervention selection (i.e., propensity score), non-attrition (i.e., probability of having outcome data), and the outcome (Glynn and Quinn, 2010; Kurz, 2021). AIPW offers several advantages compared to traditional parametric regression-based analyses. By combining models for intervention, attrition, and outcome, AIPW can control multiple potential sources of bias. Moreover, the use of nonparametric machine learning models makes AIPW an efficient estimator for attaining the smallest theoretical sampling variance without imposing additional assumptions. Thus, this approach can obtain point estimates with less bias and smaller confidence intervals with better coverage. Both AIPW and machine learning are grounded in decades of theoretical and empirical research; advances in computing power along with availability of open-source machine learning software have facilitated the application of these advanced approaches in the biomedical and behavioral sciences. The formulas used to estimate and compare BI effects across the depressed and non-depressed groups are provided in the [Supplementary Material](#).

Each component of the AIPW models was estimated using stacked ensemble machine learning with the *h2o* package (H2O.ai, 2016) in the open-source programming software R (version 4.1.1) (R Core Team, 2013). Stacked ensembles (also referred to as super learners) are comprised of algorithms that estimate the outcomes of interest (i.e., the base learners) and an algorithm that integrates estimates from the base learners to make a final estimate (i.e., the meta-learner). This approach combines the strengths of diverse algorithms based on how accurately they estimate the outcome of interest. The added flexibility can protect against model misspecification because the algorithm(s) that works best (e.g., regression without interaction vs. data-adaptive tree-based methods with complex non-parametric interactions) may depend on the estimand (e.g., intervention outcome vs. intervention selection). Nested cross-estimation was used to protect against overfitting, such that all estimates used in the AIPW were based on models trained in separate data (Zivich and Breskin, 2021). Each meta-learner selected from a pool of up to 50 base learners comprised of generalized linear model with elastic net regularization, gradient boosting machines, distributed random forests, extremely randomized trees, and multi-layer artificial neural networks, each with different tuning parameters. The code used to run the analyses is included in the [Supplementary Material](#), and a full description of the individual algorithms (including hyperparameters) is provided in the documentation for *h2o* (<https://docs.h2o.ai/h2o/latest-stable/h2o-docs/automl.html>).

3. Results

Fig. 2 summarizes the study results. AIPW estimates of the average intervention effect showed significantly greater reduction across the four drinking outcomes: 1) drinking days mean difference [95% CI], -0.05 [-0.08 , -0.02], $p < 0.001$; 2) heavy drinking days, -0.41 [-0.59 , -0.22], $p < 0.001$; 3) drinks per week -0.17 [-0.28 , -0.05], $p = .004$; and 4) drinks per drinking day -0.06 [-0.09 , -0.03], $p < .001$. The overall effects were consistent with what was

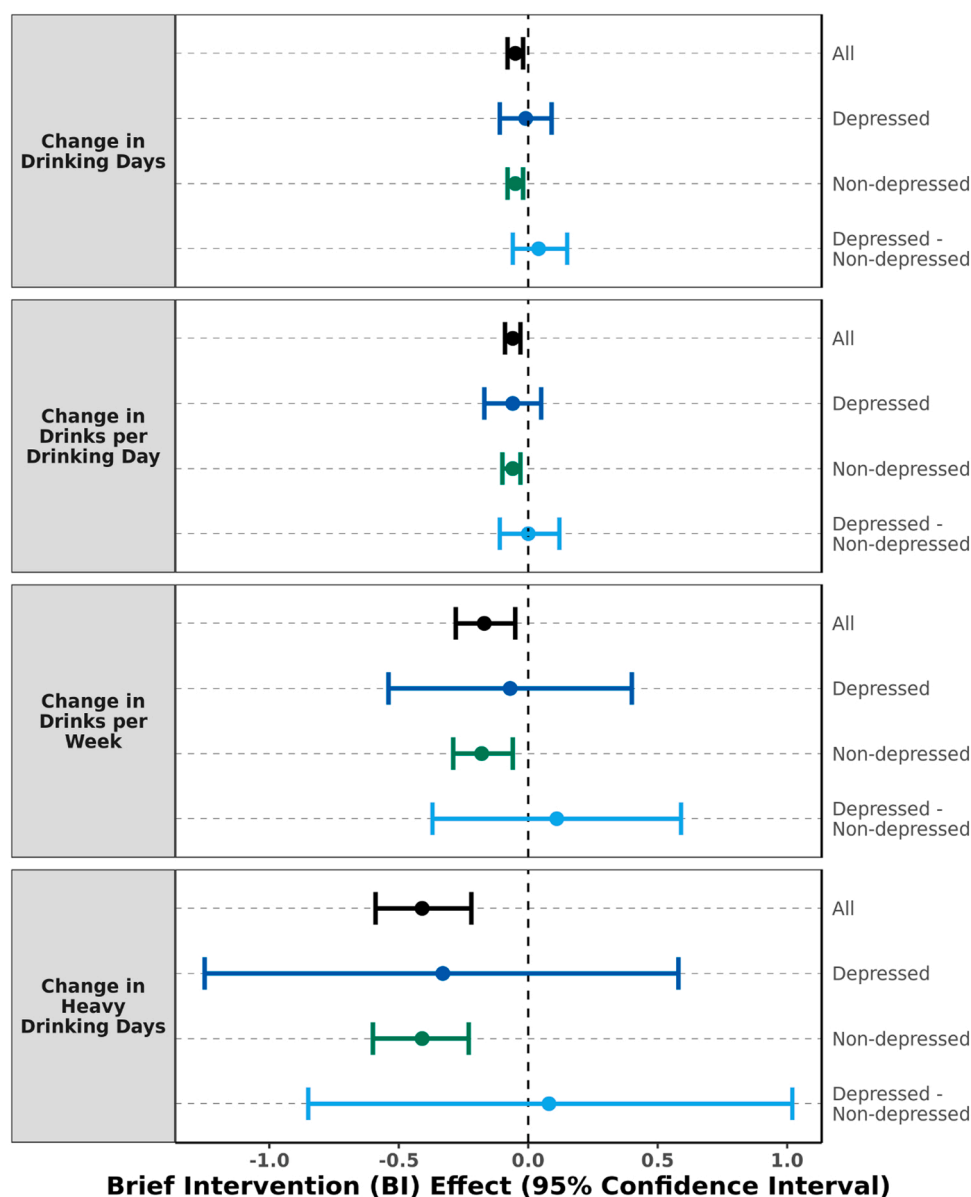


Fig. 2. Average BI effects for each 12-month alcohol use outcome. *Note.* Estimates are based on augmented inverse probability weighting models that used the complete sample of individuals that received BI ($n = 148,155$; 12,622 with depression) or did not receive BI ($n = 163,901$; 14,392 with depression).

estimated in the non-depressed subgroup (-0.41 to -0.05 , all $ps < .003$), whereas the depressed subgroup did not show significant effects (-0.33 to -0.01 , all $ps > .28$); however, comparisons between depressed and non-depressed subgroups were nonsignificant (0.00 to 0.11 , all $ps > .44$). AIPW estimates of the average intervention effect within each subgroup are provided in the [Supplementary Material](#).

4. Discussion

Consistent with prior analyses that used marginal structural models with inverse probability weights estimated by logistic regression (Chi et al., 2022), our results showed modest but robust average BI effects across four drinking outcomes using an AIPW approach with machine learning, which requires fewer assumptions to address potential confounding in intervention delivery and follow-up participation and is more robust to model misspecifications. This highlights the utility of data-adaptive approaches to estimating intervention effectiveness as delivered to hundreds of thousands of patients in real world settings, a key extension of the scientific support for BI that includes evidence from

tightly controlled randomized trials in relatively smaller samples.

Extending this approach to compare the efficacy of BI between subgroups of patients with and without depression yielded a consistent, though nonsignificant, pattern of results suggesting that BI was slightly less effective for the depressed population. As captured by the confidence intervals in Fig. 2, the intervention effect in the depressed group was nonsignificant (i.e., the estimated effects overlapped with zero). A key source of the inflated variance in the depressed group is the relatively smaller sample size (27,014 depressed vs 285,042 non-depressed); this variability impacted inference on the difference in the intervention effect. Unobserved confounders may also have an impact on estimates, though their impact on our estimate of the difference in intervention effect would require that they have differential biasing effects across subgroups (Schuler and van der Laan, 2022). Together, these results suggest that further research is needed to improve our understanding of the impact of BI on alcohol use among patients with depression.

Further research may help clarify whether there are clinical explanations for the pattern of results we observed. Given that amotivation is a core feature of depression (Grahek et al., 2019; Smith, 2013), BI may

not be sufficient for enhancing motivation to change alcohol use for patients with severe depression in general, or severe reductions in motivation in particular. There may be practice variation among primary care providers in how depression was considered when delivering BI, potentially leading to inconsistent effects. For example, it is possible that people with depression may benefit from a somewhat longer or more tailored brief intervention to reduce unhealthy alcohol use (Boniface et al., 2017; Satre et al., 2016). Additionally, some patients with depression may use alcohol to cope with negative emotional states (Magee and Connell, 2021); therefore, careful consideration of the interplay between alcohol use and depression (Boden and Fergusson, 2011) and more frequent monitoring of both outcomes (Hirschtritt et al., 2018) may be necessary to adequately address the complex needs of this subpopulation.

We note several limitations. Despite the advantages of AIPW with machine learning, any causal analysis must still rely on certain unverifiable assumptions. In our setting, the effects of interest can only be statistically identified if all confounders and common predictors of the outcome and loss to follow-up are observed and included in the analysis; there may be key unmeasured confounders that could impact results, such as depression severity, BI fidelity, and baseline motivation to change alcohol use. Additionally, we relied on patient self-report of alcohol use and there were no direct measurements of BI fidelity. Given the smaller size of the depressed subgroup, and the nonsignificance of statistical comparisons, cautious interpretation is warranted, and more research is necessary to better understand the efficacy of BI for patients with depression. Finally, we leveraged data from the EHR of a large integrated healthcare delivery system with membership that reflects the diversity of the U.S. population; further research is required to assess whether findings generalize to other healthcare systems or to uninsured populations.

5. Conclusions

We examined the impact of BI delivered in the primary care departments of a large, diverse, integrated healthcare system using AIPW with machine learning, a method that is flexible, efficient, robust, and interpretable, to compare intervention effectiveness across subgroups. On average, BI showed effectiveness in reducing unhealthy drinking, but more research is necessary to understand its impact on patients with depression, who showed a nonsignificant, though consistent, pattern of slightly weaker intervention effect.

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CRediT authorship contribution statement

Santiago Papini: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Felicia W. Chi:** Software, Data curation, Writing - original draft, Writing - review & editing. **Alejandro Schuler:** Methodology, Software, Supervision, Writing - original draft, Writing - review & editing. **Derek D. Satre:** Writing - review & editing. **Vincent X. Liu:** Resources, Writing - review & editing. **Stacy A. Sterling:**

Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109607.

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