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Differences in Sociodemographic and Alcohol-Related Clinical Characteristics Between Treatment Seekers and Non-treatment Seekers and their Role in Predicting Outcomes in the COMBINE Study for Alcohol Use Disorder

Carolina L. Haass-Koffler^{1,2,3,*}, Daria Piacentino^{3,4}, Xiaobai Li⁵, Victoria M. Long², Mary R. Lee³, Robert M. Swift^{1,6}, George A. Kenna¹, Lorenzo Leggio^{2,3,4,7,8,9,*}

¹Center for Alcohol and Addiction Studies, Department of Psychiatry and Human Behavior, Brown University, Providence, RI;

²Center for Alcohol and Addiction Studies, Department of Behavioral and Social Sciences, School of Public Health, Brown University, Providence, RI;

³Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, National Institute on Drug Abuse Intramural Research Program and National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, National Institutes of Health, Baltimore and Bethesda, MD;

⁴Center on Compulsive Behaviors, National Institutes of Health, Bethesda, MD;

⁵Biostatistics and Clinical Epidemiology Services, National Institutes of Health, Bethesda, MD;

⁶Veterans Affairs Medical Center, Providence, RI;

⁷Medication Development Program, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health, Baltimore, MD;

⁸Division of Addiction Medicine, Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD;

⁹Department of Neuroscience, Georgetown University Medical Center, Washington, DC.

Abstract

Background: One of the challenges in early stage clinical research aimed at developing novel treatments for alcohol use disorder (AUD) is that the enrolled participants are heavy drinkers, but do not seek treatment for AUD.

Aims: To compare non-treatment seekers with alcohol dependence (AD) from four human laboratory studies conducted at Brown University ($N=240$; 65.4% male) to treatment seekers with

*Correspondence: Carolina L. Haass-Koffler, Pharm.D., Center for Alcohol and Addiction Studies, Department Psychiatry and Human Behavior, Brown University, 121 South Main Street, Providence, RI 02912, Phone: 401-863-6630, carolina_haass-koffler@brown.edu, Lorenzo Leggio, M.D., Ph.D., [Clinical Psychoneuroendocrinology and Neuropsychopharmacology](#) Section, NIDA IRP and NIAAA DIBCB, National Institutes of Health, 251 Bayview Blvd, Baltimore, MD 21224, Phone: 443-740-2293, lorenzo.leggio@nih.gov.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

AD from the multisite COMBINE study ($N=1383$; 69.1% male) across sociodemographic and alcohol-related clinical variables; and to evaluate if the variables that significantly differentiate the two samples predict the three main COMBINE clinical outcomes: time to relapse, percent days abstinent (PDA), and good clinical outcome.

Methods: Sample characteristics were assessed by parametric and non-parametric testing. Three regression models measured the association between the differing variables and the three main COMBINE clinical outcomes.

Results: The non-treatment seekers, compared to the treatment seekers, were more ethnically diverse, less educated, single, and working part-time or unemployed ($p's < 0.05$); they met fewer DSM-IV AD criteria and had significantly lower scores on alcohol-related scales ($p's < 0.05$); they were less likely to have a father with alcohol problems ($p < 0.0001$), had a significantly earlier age of onset and longer duration of AD ($p's < 0.05$); they also had significantly more total drinks, drinks per drinking day (DPDD), heavy drinking days (HDD), and lower PDA in the 30 days prior to baseline ($p's < 0.0001$ – < 0.05). Having more HDD in the 30 days prior to baseline predicted all of the three COMBINE clinical outcomes. All the other characteristics mentioned above that differed significantly between the two groups predicted at least one of the three COMBINE clinical outcomes, except for level of education, age of onset, and duration of AD.

Conclusions: The observed differences between groups should be considered in efforts across participant recruitment at different stages of the development of new treatments for AUD.

Keywords

Alcohol use disorder; alcohol dependence; treatment seekers; non-treatment seekers; COMBINE; randomized controlled trial (RCT); medication development

Introduction

In the United States, over 15.1 million adults are diagnosed with alcohol use disorder (AUD) (NIAAA, 2018), yet less than 8% are treated for AUD, with only 4% receiving pharmacotherapy (Park-Lee et al., 2016, Kranzler and Soyka, 2018, Witkiewitz et al., 2019).

While pharmacotherapies to treat AUD are useful means of treatment, there are currently only three Food and Drug Administration (FDA)-approved medications to treat AUD – disulfiram, naltrexone (oral and long-acting injectable formulations) and acamprosate. These medications are effective but show small or moderate effect sizes (Litten et al., 2012). This low response is likely a consequence of the heterogeneity of the AUD population (Enoch et al., 2009).

A factor that may critically influence the heterogeneity of this population is the motivation to seek treatment for AUD. In the clinical research setting, participants are often selected based on their treatment-seeking status (non-treatment seekers and treatment seekers) for methodological and ethical reasons, particularly when human laboratory studies include the administration of alcohol (Enoch et al., 2009). However, differences have been found between non-treatment and treatment seekers across sociodemographic characteristics, such as sex, age, level of education, employment, and marital status (Locastro et al., 2008, Ray et

al., 2017, Rohn et al., 2017, Lee et al., 2019). These populations have also been found to differ in alcohol-related clinical characteristics, such as age of onset and duration of AUD, or number of drinks consumed per day (Ray et al., 2017). They may also differ in characteristics that go beyond the quantity of alcohol consumption, such as history of trauma, personality traits, impulsivity, aggressive behavior, cognition, mood, and liver enzyme levels, which are generally associated with excessive alcohol use (Rohn et al., 2017). Identifying differences between populations of varying treatment-seeking statuses is fundamental when designing and testing interventions for AUD. Recently, by using a machine learning algorithm, it was possible to identify a cluster of neuropsychological, behavioral, and laboratory variables that accurately predict whether AUD individuals seek treatment, or not, for their alcohol problems (Lee et al., 2019). These are relevant aspects that need consideration in the context of medication development, given that early phase human laboratory studies often enroll non-treatment seekers, but the final intent is to use these medications, if proven to be effective, in treatment seekers.

Additionally, non-treatment and treatment seekers have different motivations for being in research studies. They exhibit different opinions surrounding AUD medications, and treatment-naïve or non-treatment-seeking individuals, overall, are less motivated to adhere to medications, with a consequent effect on treatment outcomes and medication efficacy measures in AUD research (Locastro et al., 2008). Thus, when designing early stage trials for AUD medications, it is important to consider, in addition to the aforementioned sample differences, the underlying construct of readiness to change, which may influence drinking behavior (Witkiewitz et al., 2015).

Among the studies briefly summarized above, one of them (Ray et al., 2017) compared non-treatment-seeking participants with alcohol dependence (AD) from four human laboratory studies conducted at the University of California, Los Angeles (UCLA) to treatment-seeking participants with AD from the COMBINE study, a multisite randomized controlled trial (RCT) that evaluated naltrexone and acamprosate, with or without a combined behavioral intervention (CBI) (Anton et al., 2006). The psychiatric assessment for all studies was conducted according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) by the Structured Clinical Interview for DSM Disorders (SCID-IV), Module E (American Psychiatric Association, 1994). The UCLA non-treatment seekers were found to be more likely men, younger, African American, less educated, and in a committed relationship (but not married) than the COMBINE treatment seekers. Additionally, the UCLA non-treatment seekers, compared to the COMBINE treatment seekers, endorsed less symptoms of DSM-IV AD, they scored significantly lower on the Alcohol Dependence Scale (ADS) (Skinner and Allen, 1982), the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1996), the Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised (CIWA-Ar) (Sullivan et al., 1989), and the Drinker Inventory of Consequences (DrInC-2R) (Miller, 1995), and they had significantly less total drinks and drinks per drinking day (DPDD), as assessed through the Timeline Followback (TLFB) (Sobell and Sobell, 1992). Non-treatment seekers, although not actively seeking treatment, also showed the desire to cut down on drinking, as demonstrated by their Readiness to Change score on the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) (Miller and Tonigan, 1997). The UCLA work found that nearly all the

characteristics that differed between the non-treatment and treatment seekers were predictive of at least one of the main treatment outcomes of the COMBINE study. These include, over the course of the 16-week treatment period: time to first heavy drinking day (HDD, 5 drinks/day for males and 4 drinks/day for females), also known as time to relapse; percent days abstinent (PDA); and good clinical outcome (GCO), defined as abstinence or moderate drinking without adverse consequences on the DrInC-2R (Anton et al., 2006).

The advancement of medications for AUD is based not only on the specificity of neurobiological systems used as pharmacological targets, but also on the optimization of translational paradigms from human laboratory studies to larger RCTs (Lapchak, 2012, Witkiewitz et al., 2015). The goal of this study was to compare non-treatment seekers enrolled in human laboratory studies with treatment seekers from a large RCT. Specifically, the present study sought to analyze and compare sociodemographic and alcohol-related clinical characteristics between the cohort of non-treatment-seeking individuals with AD, from four human laboratory studies conducted at Brown University, and the cohort of treatment-seeking individuals with AD, from the multisite COMBINE study. Furthermore, this study aimed to evaluate if the characteristics that differed significantly between the two samples predicted the main COMBINE study clinical outcomes. This aspect not only is critical to determine the methodological scientific rigor of secondary analyses, but it also highlights the importance of evaluating the enrollment process of participants for AUD studies from different geographical locations within the United States. The discrete geographical enrollment from a single site limits the generalization of findings (Bellomo et al., 2009), therefore this study will build additional information on the clinical applicability of the AUD medication development process from single-site trials to larger multisite RCTs.

Methods

Participants

Brown University Studies: Non-Treatment Seekers—Individuals with AD, but not seeking treatment, took part in one of four AUD human laboratory studies conducted at Brown University between 2008–2020, which tested the efficacy on alcohol-related outcomes of: intravenous ghrelin ([NCT01190085](#)) (Leggio et al., 2014); ondansetron and sertraline ([NCT01113164](#)) (Kenna et al., 2014); aripiprazole and topiramate (alone and combined) ([NCT00884884](#)) (Haass-Koffler et al., 2018); and mifepristone after a stress-inducing dose of yohimbine ([NCT02243709](#)) (ongoing study). All studies were approved by the Brown University Institutional Review Board. Details of the studies and their eligibility criteria are provided here and summarized in Table 1. All participants ($N=240$) were recruited from the Rhode Island area via advertisements in public transportation, newspapers, and online social media. They were all 21 years old, in good health, met DSM-IV criteria for current AD, and consumed 35 drinks/week (males) or 28 drinks/week (females) in the 90 days prior to baseline. Exclusion criteria included: a history of DSM-IV Axis I diagnosis other than AD and nicotine dependence; pregnancy or lactation; positive urine drug screen at baseline for any illegal substance; drugs that interacted with study medications; and significant alcohol withdrawal symptoms.

The COMBINE Study: Treatment Seekers—Treatment-seekers with AD considered in the present study were enrolled between 2001–2004 in the COMBINE study, a national multisite RCT sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) ([NCT00006206](#)) (Anton et al., 2006). This RCT evaluated the ability of combinations of 100 mg/day of naltrexone, 3 g/day of acamprosate, placebo, and combined behavioral intervention (CBI) to increase alcohol abstinence over a 16-week period in treatment-seeking individuals with AD. There were nine total treatment groups consisting of combinations of naltrexone, acamprosate, both naltrexone and acamprosate, with or without placebo, and with or without CBI, and a group that received only CBI and no medication or matching placebo. Description of the COMBINE study and its eligibility criteria are provided here and summarized in Table 1. Eligible participants ($N=1383$) were recruited from 11 academic sites across the United States, including Brown University. They were all 18 years old, sought treatment for alcohol problems, met DSM-IV criteria for current AD, and had consumed >21 drinks/week (males) or >14 drinks/week (females), with at least two HDD during a consecutive 30-day period, within 90 days prior to baseline. Participants also had to be abstinent from alcohol for 4–21 consecutive planned days prior to randomization, with no withdrawal symptoms. Exclusion criteria included: a history of other DSM-IV substance abuse or dependence disorder, other than nicotine or cannabis, in the prior 90 days (6 months for opioid abuse), as indicated by self-report or by positive urine drug screen; a current DSM-IV psychiatric disorder requiring medication; or an unstable medical condition. Primary results found that naltrexone, CBI, or their combination significantly reduced drinking behavior, whereas acamprosate showed no evidence of efficacy, with or without CBI (Anton et al., 2006).

Sample Characteristics

Sociodemographic Characteristics—Baseline sociodemographic characteristics were collected from participants across all studies. Sex, age, race/ethnicity, level of education, marital status, employment status, and both systolic (SBP) and diastolic (DBP) blood pressure were part of our analyses.

Alcohol-Related Clinical Characteristics—Baseline alcohol-related clinical characteristics were assessed prior to any medication administration/pharmacological manipulation specific to the four Brown University studies or the COMBINE study, therefore none of them were influenced by the subsequent interventions. In all studies, AD diagnosis was made according to the DSM-IV using the SCID-IV (First and Gibbon, 2004), a semi-structured interview administered by trained clinicians that provides the number of DSM-IV criteria for AD met by an individual. The severity of AD was measured using the ADS (Skinner and Allen, 1982), a 25-item self-administered questionnaire that provides an overall score by assessing alcohol withdrawal symptoms, impaired control over drinking, awareness of a compulsion to drink, increased tolerance to alcohol, and salience of drink-seeking behavior. Participants also completed the OCDS (Anton et al., 1996), a 14-item self-administered measure that investigates the cognitive and behavioral aspects of alcohol craving. The OCDS is sensitive to, and specific for, the obsessive and compulsive characteristics of drinking-related thoughts, urges to drink, and the ability to resist these thoughts and urges. It is a reliable monitoring tool for AUD treatment and has predictive

validity for relapse. Total OCDS score was calculated. Signs and symptoms of alcohol withdrawal were assessed using the CIWA-Ar (Sullivan et al., 1989), a 10-item self-administered questionnaire that quantifies and monitors the withdrawal process in clinical settings by measuring agitation, anxiety, auditory disturbances, clouding of sensorium, headache, nausea/vomiting, paroxysmal sweats, tactile disturbances, tremor, and visual disturbances. Furthermore, participants filled out a baseline DrInC-2R (Miller, 1995), a 40-item self-administered inventory that measures the adverse consequences of drinking, unconfounded with other dimensions – consumption patterns, help-seeking, and dependence – by focusing on five areas: physical, interpersonal, intrapersonal, impulse control, and social responsibility. Additionally, the family (mother/father) history of alcohol problems was collected, as it has been shown to be an indicator of increased risk and severity of AUD (Farmer et al., 2018). Other alcohol-related clinical characteristics included in our analyses were the age of onset and duration of AD, as well as the total number of drinks, DPDD, HDD, and PDA in the 30 days prior to baseline. The latter were calculated with the TLFB (Sobell and Sobell, 1992), a drinking assessment method that measures, retrospectively, an individual's daily alcohol intake up to 360 days from the interview date. It can generate variables that provide a relatively accurate portrayal of an individual's drinking (e.g., pattern, variability, and magnitude of drinking). Standard Drink Units (SDUs), equal to 10 g of alcohol, were calculated for all studies to quantify a standard number of drinks that participants consumed per day.

Statistical Analysis

Missing data were relatively uncommon, yet participants of the Brown University studies and of the COMBINE study had missing data for specific variables. Given the multiple time points, the mixed models used for the analyses adjusted for missing data. To compare the sociodemographic and alcohol-related clinical characteristic between the non-treatment seekers from the Brown University studies and the treatment seekers from the COMBINE study, we carried out: i) the *Chi*-squared test (χ^2) for categorical variables; ii) the parametric two-sample *t*-test (*t*) or the non-parametric Wilcoxon rank-sum test (*W*) for continuous variables, as deemed appropriate, after checking the normality assumption. Effect size measures, such as Cramer's *V*, Cohen's *d*, Vargha and Delaney *A* (*VDA*), and the respective 95% confidence intervals (*CI*s), were calculated for the three aforementioned tests using Rstudio (packages psych, effsize, and rcompanion) (RStudio Team. RStudio: Integrated Development for R. Boston, MA: URL RStudio, Inc., 2015). For variables that significantly differed ($p < 0.05$) between the two study samples, we further examined their effects on the three main COMBINE clinical outcomes. A Cox proportional hazards model, a linear mixed-effects model, and a logistic regression model were fitted to the COMBINE data, including treatment arm ($2 \times 2 \times 2$, acamprosate $\times$ naltrexone $\times$ CBI), the study sites, the PDA in the 30 days prior to baseline, and the selected covariate. The Cox proportional hazards model was fitted for time to relapse, providing an estimate of the hazard ratio and its 95% *CI*. Adjusted hazard ratios were computed to estimate the effect sizes over and above treatment effects. The linear mixed-effects model was fitted for PDA after the 16-week treatment period, providing the fixed effect regression coefficient (*B*) and its 95% *CI*. GCO was analyzed with a binomial logistic regression model. Adjusted odds ratios (ORs) were computed controlling for treatment effects. Benjamini-Hochberg false discovery rate (FDR)

<0.01 was considered as statistically significant. Analyses were performed using the Statistical Analysis Software SAS® (SAS software for Windows, Version 9.4, Cary, NC: SAS Institute Inc., 2013), unless stated otherwise.

Results

The present study included 240 non-treatment seekers with AD (i.e., participants from the Brown University studies) and 1383 treatment-seeking with AD (i.e., participants from the COMBINE study). The main sociodemographic characteristics of the two samples are reported in Table 2. Sex and age were comparable between the two samples. The majority of non-treatment and treatment seekers were of male sex (65.4% and 69.1%, respectively). The Brown non-treatment seekers were slightly younger than the COMBINE treatment seekers (mean age of 42.4 years and 44.4 years, respectively) at a trend level ($p=0.065$). Race/ethnicity, years of education, marital status, and employment status were not equally represented between the two samples. The Brown non-treatment seekers, compared to the COMBINE treatment seekers, identified themselves in a significantly higher proportion as African American or a race other than Caucasian ($p<0.001$), had a significantly lower median number of years of education ($p<0.05$), reported their relationship status in a significantly higher proportion as single ($p<0.001$), and were in a significantly higher proportion working part-time or unemployed ($p<0.001$). Both systolic and diastolic blood pressures did not differ significantly between the two samples.

The Brown non-treatment seekers met significantly fewer DSM-IV AD criteria than the COMBINE treatment seekers, with a median number of 4 criteria and 6 criteria, respectively ($p<0.05$). The main alcohol-related clinical characteristics of the two samples are reported in Table 3. The Brown non-treatment seekers differed significantly from the COMBINE treatment seekers on all the assessed alcohol-related characteristics, except for their likelihood of having a mother with alcohol problems. Furthermore, their likelihood of having a father with alcohol problems was much more significant ($p<0.0001$). The Brown non-treatment seekers had significantly lower ADS, OCDS, CIWA-Ar, and baseline DrInC-2R median scores than the COMBINE treatment seekers (p 's<0.05). They had a significantly earlier median age of onset of AD ($p<0.05$) and a significantly longer median duration of AD ($p<0.05$). Furthermore, in the 30 days prior to baseline, they had a significantly higher median number of total drinks, DPDD, and HDD (p 's from <0.0001 to <0.05) and a significantly lower median PDA ($p<0.05$) than the COMBINE treatment seekers.

After identifying the sociodemographic and alcohol-related clinical characteristics that differed significantly between the Brown non-treatment seekers and the COMBINE treatment seekers, we tested whether they predicted the three main COMBINE clinical outcomes, i.e., time to relapse, PDA, and GCO (FDR<0.01), during the 16-week treatment period. As shown in Table 4, time to relapse in the COMBINE study was significantly predicted by male sex ($p<0.001$), being single ($p=0.007$), number of DSM-IV AD criteria ($p<0.001$), and OCDS total score ($p<0.001$), as well as total drinks ($p<0.001$) and HDD ($p<0.001$) in the 30 days prior to baseline. PDA was significantly predicted by being of American Indian/Alaskan Native, Asian American/Pacific Islander, or bi-/multi-racial

ethnicity ($p<0.001$), ADS total score ($p=0.001$), baseline DrInC-2R total score ($p<0.001$), having a father with alcohol problems ($p<0.001$), and DPDD ($p<0.001$) and HDD ($p<0.001$) in the 30 days prior to baseline. Lastly, probability of GCO was significantly predicted by currently working full-time ($p=0.001$), CIWA-Ar total score ($p=0.002$), and baseline DrInC-2R score ($p<0.001$), as well as total drinks ($p<0.001$) and HDD ($p<0.001$) in the 30 days prior to baseline.

Lastly, although we did not aim to formally replicate previous data analysis, we assessed the significant differences between the non-treatment and treatment seekers from this study and from the studies by: Ray and colleagues (2017), who compared UCLA non-treatment seekers with SCID-IV AD ($N=213$) to the COMBINE treatment seekers ($N=1383$); Rohn and colleagues (2017), who compared non-treatment ($N=150$) and treatment seekers ($N=528$) with SCID-IV AD, participating in research screening protocols at the National Institute on Alcohol Abuse and Alcoholism (NIAAA); and Lee and colleagues (2019), who compared non-treatment ($N=169$) and treatment seekers ($N=609$) with SCID-IV AD, taking part in screening and evaluation protocols at the NIAAA. As illustrated in Table 5, where we highlight the comparable findings from this study and any of the three other studies, age did not significantly differ between non-treatment and treatment seekers, except for one study (Ray et al., 2017). In all four studies, African Americans were significantly more represented, and Caucasians were significantly less represented, in non-treatment seekers than treatment seekers. All other races were significantly more represented in non-treatment seekers than treatment seekers in both this study and the study by Ray and colleagues (2017). As for marital status, the latter two studies found that the non-treatment seekers from Brown University and UCLA were significantly less likely to be in a committed relationship or to have been married/divorced, respectively, compared to the treatment seekers from the COMBINE study. All four studies showed that the non-treatment seekers met less SCID-IV AD criteria than the treatment-seekers. In addition, in this study and in the study by Ray and colleagues (2017), non-treatment seekers scored significantly lower on the ADS, OCDS, and Baseline DrInC-2R than treatment seekers. Finally, this study and the studies by Rohn and colleagues (2017) and by Lee and colleagues (2019) found that non-treatment seekers were significantly less likely to have a family history of alcohol problems than treatment seekers.

Discussion

Demographic and clinical differences between treatment seekers and non-treatment seekers with AUD have been hypothesized to influence AUD treatment effectiveness (Witkiewitz et al., 2015). These differences may impact the translational efforts to move treatments from early phase human studies, which often enroll non-treatment seekers, to larger clinical trials, which typically enroll treatment seekers. The present study compared individuals with AD who were not interested in seeking treatment to individuals with AD who were seeking treatment and identified several sociodemographic and alcohol-related clinical differences, similarly to previous research (Ray et al., 2017, Rohn et al., 2017, Lee et al., 2019). In particular, following-up on Ray and colleagues' work (2017), where non-treatment seekers enrolled in four human laboratory studies at UCLA were compared to the treatment seekers from the COMBINE study, here we compared non-treatment seekers enrolled in four human laboratory studies at Brown University to the COMBINE cohort, with the latter being a large

clinical research sample, possibly representative of the AUD population that will use approved medications in clinical practice. All data used herein were related to baseline characteristics, therefore none of these data were influenced by subsequent medication administration or pharmacological manipulation.

In regard to sociodemographic characteristics, the Brown non-treatment seekers were significantly more ethnically diverse, less educated, less likely to be in a committed relationship, and more likely to be working part-time or unemployed compared to the COMBINE treatment seekers. Concerning alcohol-related clinical characteristics, the Brown non-treatment seekers met significantly fewer DSM-IV criteria for AD than the COMBINE treatment seekers. This difference reinforces the hypothesis that non-treatment seekers have a less severe AD presentation than treatment seekers (Ray et al., 2017). Individuals with a lesser severity of the disorder, fewer adverse consequences of alcohol drinking, and a lower impact on health-related quality of life are less likely led to seek treatment. As expected, the Brown non-treatment seekers had a lesser severity of AD on the ADS, fewer obsessive thoughts about alcohol and compulsive behaviors to use alcohol on the OCDS, fewer CIWA-Ar withdrawal symptoms, and fewer DrInK-2R adverse consequences of drinking than the COMBINE treatment seekers. Additionally, the Brown non-treatment seekers were less likely to have a father with an alcohol problem, had an earlier age of onset of AD, and a longer duration of AD than the COMBINE treatment seekers. Lastly, the Brown non-treatment seekers had significantly more total drinks, drinks per drinking day, heavy drinking days, and fewer number of days abstinent in the 30 days prior to baseline than the COMBINE treatment seekers. This observation could be explained by the fact that these individuals are not looking for treatment, thus they lack the motivation to cut back on, or quit, drinking prior to study enrollment, different from treatment seekers, who may have cut back on drinking prior to study participation. Finally, as the COMBINE treatment seekers were more likely to be married compared to the Brown non-treatment seekers, marriage may represent a motivation for treatment seeking. This characteristic should also be taken into consideration when recruiting participants in human laboratory studies. No significant differences were found between the two samples in terms of sex, age, blood pressure, and the likelihood of having a mother with an alcohol problem.

The results of our study substantially replicate the previous work by Ray et al. (2017), which found that the UCLA non-treatment seekers differed significantly from the COMBINE treatment seekers in several sociodemographic and clinical characteristics. Yet, our non-treatment seekers were older and less educated than the UCLA ones, possibly due to cultural differences between Providence (RI) and Los Angeles (CA). They were less ethnically diverse than the UCLA non-treatment seekers, and this could be explained by California being one of the most ethnically diverse states of the United States (Lee et al., 2017). Also, while we found no significant sex differences between our non-treatment seekers and the COMBINE treatment seekers, the UCLA studies enrolled significantly more men than the COMBINE study. Furthermore, the Brown non-treatment seekers had lower ADS and OCDS scores than the UCLA ones, possibly due to an underreporting of symptoms or simply an overall lesser severity of AD in the Brown sample. Our non-treatment seekers had a significantly longer duration of AD than the UCLA non-treatment seekers. This difference could be ascribed to the Brown participants having an earlier age of onset of AD or a lower

level of education than the UCLA participants. Low educational attainment has been linked to earlier onset, longer duration, and more exacerbations of AD (Curran et al., 1999). Besides the characteristics evaluated in the UCLA work (Ray et al., 2017), we assessed additional characteristics, including employment status, systolic and diastolic blood pressure, the likelihood of having a father or mother with alcohol problems, the age of onset of AD, and the number of heavy drinking days and percent days abstinent in the 30 days prior to baseline. Of note, a family history of AD is associated with help seeking and higher mental health service use. Furthermore, a history of help seeking for alcohol problems among family members of offspring is associated with the offspring's own alcohol problem recognition (True et al., 1999, Milne et al., 2009, Glass et al., 2015). The results of the present study are also consistent with a previous study that compared the physiological and psychological characteristics of NIAAA non-treatment and treatment seekers with SCID-IV AD (Rohn et al., 2017). In this study, non-treatment seekers differed from treatment seekers beyond sociodemographic and alcohol-related clinical characteristics, and manifested significantly less impairment in terms of personality, impulsivity, trauma, stress, cognition, mood, and liver enzyme levels. While our data do not allow for direct replication of the latter findings, the two studies concur in noting that non-treatment and treatment seekers with AD exhibit significantly different phenotypes. The identification of these phenotypes is crucial, as they may influence outcomes of early phase studies and are potential confounders in assessing the efficacy of new treatments for AUD. Our results also partially replicate those of a recent study that aimed to classify DSM-IV AD individuals based on their treatment-seeking status to implement a targeted treatment approach (Lee et al., 2019). Machine learning, more specifically a decision tree classifier, was used to reduce 178 neuropsychological, behavioral, and laboratory variables to a subset of 10 variables that, together, best distinguished NIAAA non-treatment and treatment seekers. The advantage of machine learning, compared to traditional regression analysis, consists in its ability to overcome the issue of multicollinearity between variables and handling missing data, as well as to provide outcomes granted not only with predictive, but also with clinical value.

Another aim of our study was to test whether the characteristics that differed significantly between the Brown non-treatment seekers and the COMBINE treatment seekers predicted any of the three main COMBINE study clinical outcomes, i.e., time to relapse, PDA, and GCO. Other studies have found that specific participant characteristics are moderators or predictors of treatment outcomes in the COMBINE study (Subbaraman et al., 2013, Gueorguieva et al., 2015, Worley et al., 2015, Ray et al., 2017). In particular, the UCLA work (Ray et al., 2017) found that nearly all the sociodemographic and clinical characteristics differing significantly between the UCLA non-treatment seekers and the COMBINE treatment seekers predicted at least one COMBINE study outcome. Our study replicated these findings. Being male, single, of American Indian/Alaskan Native, Asian American/Pacific Islander, or bi-/multi-racial ethnicity, working full time, having more DSM-IV AD criteria, AD of greater severity, higher OCDS obsessive-compulsive scores, more CIWA-Ar withdrawal symptoms, more baseline DrInK-2R adverse consequence of drinking, a father with alcohol problems, and more total drinks and DPDD in the 30 days prior to baseline predicted at least one COMBINE study outcome. Having more HDD in the 30 days prior to baseline predicted all three COMBINE study outcomes. Our study further

supports the assumption that non-treatment and treatment seekers have critical differences capable of influencing the effectiveness of AUD treatments, with non-treatment seekers presenting with less severe AD than treatment seekers. Given that current research on AUD treatment and interventions depends on translating results obtained in the non-treatment-seeking population to treatment seekers, to improve the reliability of early stage human laboratory studies, it would be advisable to enroll participants with more severe AD.

It is important to consider that the distinction between non-treatment seekers and treatment seekers is rather simplistic, since it is based on self-reported assessment at screening and a dichotomous split may not follow the more complex stages of changes driven by motivation to quit or reduce alcohol consumption (Prochaska et al., 1986, Prochaska et al., 1992, DiClemente, 2018). Furthermore, it is important that this self-reported, dichotomous distinction is made in the context of specific clinical research settings, as opposed to patient care settings. In human laboratory studies, non-treatment seekers might have an initial (unconscious) desire to at least explore their alcohol problems. On the other hand, treatment seekers may be prone to be enrolled for reasons outside their real desire to seek treatment. As such, willingness for change may not be simply related to sociodemographic and AUD-related characteristics, but should be considered in a more complex and dynamic change process (DiClemente et al., 2009). The limitation of the dichotomous status assigned to non-treatment and treatment seekers also casts important ethical considerations, since studies that enroll non-treatment seekers often include alcohol administration (Enoch et al., 2009). Including additional measures to describe the treatment status of individuals interested in participating in alcohol RCTs may help improve a wider categorical characterization (e.g., readiness rules from 0 to 10). Questionnaires should be administered that can improve readiness to change in AUD; ones that can capture pre-contemplation, contemplation, and action stage (Heather and Rollnick, 1993, Kim et al., 1998, Kim et al., 2007).

Similarly, in smoking cessation human laboratory studies, the limited screening procedures that include unmotivated and motivated to abstain (i.e., treatment and non-treatment seekers) have demonstrated insensitivity to nicotine replacement and pharmacotherapies, which are effective in clinical trials for smoking cessation (Perkins et al., 2006). Human laboratory studies are based on robust paradigms. However, often the study medication effect on abstinence symptoms, tested in a short cessation period, has limited clinical predictive validity. Also, the small sample sizes of these laboratory studies often do not have the power to detect statistical difference between study medication and placebo (Perkins, 2014), for a focused review see: (Perkins and Lerman, 2014).

The present study has a number of limitations. First, there were missing data. Yet, they were relatively uncommon in the COMBINE study, except for baseline DrInC-2R, and in the four Brown University parent studies, in regard to all the sociodemographic, and most of the alcohol-related, clinical characteristics. Only some Brown University studies missed data for specific measures (i.e., blood pressure, ADS, and baseline DrInC-2R). We adjusted for the missing data, deriving from multiple time points, by using mixed models. Another limitation is the difference in sample size between the Brown University and COMBINE studies. The COMBINE study, a multisite trial, collected data from considerably more participants than the four Brown University human laboratory studies. To control for this limitation, we

included the effect sizes in the statistical analysis. Finally, it must be noted that the COMBINE study was conducted in 11 sites across the United States over four years, whereas the four Brown studies were conducted in one single site over 10 years. Environmental issues related to the differences in geographic locations and time lapse are important to note.

Conclusions

This study assesses the specific sociodemographic and alcohol-related clinical characteristics differing between non-treatment-seeking and treatment-seeking participants in studies for AUD and highlights their clinical significance. Overall, it supports the notion that treatment seekers have a more severe AD presentation than non-treatment seekers. The observed differences between samples should be considered and addressed to help inform future research study enrollment, promote greater agreement across stages of AUD treatment development, and improve the translation of findings from early phase research to clinical practice.

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Highlights

- Non-treatment-seeking individuals with alcohol dependence (AD) participated in human laboratory studies at Brown University.
- Treatment-seeking individuals with AD participated in the multisite COMBINE study.
- Multiple characteristics (e.g., education, age of onset of AUD, and amount of alcohol consumed) were significantly different between non-treatment and treatment seekers, and predicted at least one of the three main clinical outcomes of the COMBINE study (i.e., time to first heavy drinking day, percent days abstinent, and good clinical outcome).

Table 1.

Description of the Brown parent studies and the COMBINE study.

Medication	Participants	N	Clinicaltrials.gov ID	References
Total		241		
Exogenous Intravenous Ghrelin Administration	Non-treatment seekers	45	NCT01190085	(Leggio et al., 2014)
Ondansetron/Sertraline		81	NCT01113164	(Kenna et al., 2014)
Topiramate/Aripiprazole		91	NCT00884884	(Haass-Koffler et al., 2018)
Mifepristone		24	NCT02243709	Ongoing
COMBINE (Naltrexone/Acamprosate)	Treatment seekers	1383	NCT00006206	(Anton et al., 2006)

Table 2.

Sociodemographic characteristics of the Brown non-treatment seekers and the COMBINE treatment seekers.

Variable		Non-Treatment Seekers mean (SD), median (IQR) or N (%)	Treatment Seekers mean (SD), median (IQR) or N (%)	N per sample	Test	P	Effect Size [95% CI]
Sex (Male)		157 (65.4)	955 (69.1)	240/1383	$\chi^2=1.253$	0.263	-0.03 [-0.01, -0.05]
Age (Years)		42.43 (10.98)	44.43 (10.19)	240/1383	$t=-2.78$	0.065	0.54 [0.52, 0.56]
Race/Ethnicity	Caucasian	132 (55)	1062 (76.8)	240/1383	$\chi^2=106.34$	<0.001	0.26 [0.23, 0.28]
	African American	67 (27.9)	109 (7.9)				
	Hispanic/Latino	17 (7.1)	155 (11.2)				
	Other	24 (10.0)	57 (4.1)				
Education (Years)		13 (3)	14 (4)	240/1356	$W=0.0001$	<0.05	0.62 [0.59, 0.64]
Marital Status	Single	120 (50.4)	384 (27.8)	238/1382	$\chi^2=6.425$	<0.001	0.31 [0.29, 0.34]
	Married	28 (11.8)	581 (42.0)				
	Separated	11 (4.6)	60 (4.3)				
	Divorced	36 (15.1)	287 (20.8)				
	Widow(er)	9 (3.8)	11 (0.8)				
	Cohabitant	32 (13.5)	37 (2.7)				
	Partner	2 (0.8)	22 (1.6)				
Employment Status	Currently working full-time	41 (17.1)	838 (60.9)	240/1377	$\chi^2=6.425$	<0.001	0.33 [0.30, 0.35]
	Currently working part-time	64 (26.7)	144 (10.4)				
	Retired	15 (6.2)	85 (6.2)				
	Unemployed	93 (38.8)	207 (15.0)				
	Other	27 (11.2)	103 (7.5)				
SBP (mmHg)		129.93 (17.13)	132.65 (17.77)	120/1371	$t=-1.62$	0.103	0.77 [0.72, 0.81]
DBP (mmHg)		83.44 (11.84)	83.45 (11.43)	120/1371	$t=-0.01$	0.761	0.74 [0.69, 0.87]

Significant *p*-values in **bold**. Other Race/Ethnicity=American Indian/Alaskan Native, Asian American/Pacific Islander, Bi- or Multi-Racial; Other Employment Status=Homemaker, Disabled; DBP=Diastolic Blood Pressure; SBP=Systolic Blood Pressure; CI=Confidence Interval;

IQR=Interquartile Range; *P*=*P*-value; *SD*=Standard Deviation; *t*=Student's *t*-test; *W*=Wilcoxon rank-sum test; χ^2 =Chi-squared test.

Table 3.

Alcohol-related clinical characteristics of the Brown non-treatment seekers and the COMBINE treatment seekers.

Variable	Non-Treatment Seekers mean (<i>SD</i>), median (<i>IQR</i>) or <i>N</i> (%)	Treatment Seekers mean (<i>SD</i>), median (<i>IQR</i>) or <i>N</i> (%)	<i>N</i> per sample	Test	<i>P</i>	Effect Size [95% <i>CI</i>]
DSM-IV AD Criteria (Number)	4 (3)	6 (2)	240/1383	$W=0.0001$	<0.05	0.85 [0.83, 0.87]
ADS (Total Score)	9 (9)	16 (10)	158/1378	$W=0.0001$	<0.05	0.83 [0.80, 0.86]
OCDS (Total Score)	16 (12)	27 (11)	171/1383	$W=0.0001$	<0.05	0.86 [0.83, 0.88]
CIWA-Ar (Total Score)	0 (1)	1 (3)	238/1380	$W=0.0001$	<0.05	0.68 [0.65, 0.71]
BL DrInC-2R (Total Score)	19 (22)	45 (28)	157/1381	$W=0.0001$	<0.05	0.87 [0.84, 0.90]
Father with Alcohol Problems (Yes)	88 (36.7)	675 (51.7)	240/1305	$\chi^2=18.39$	<0.0001	0.11 [0.09, 0.13]
Mother with Alcohol Problems (Yes)	69 (28.7)	306 (22.9)	240/1335	$\chi^2=3.809$	0.059	-0.04 [-0.02, -0.06]
Age of onset of AD (Years)	22 (12)	29 (17)	209/1192	$W=0.0001$	<0.05	0.75 [0.71, 0.78]
Duration of AD (Years)	17 (19)	12 (16)	209/1192	$W=0.0001$	<0.05	0.55 [0.51, 0.59]
Total drinks 30 days prior to BL (Number)	192.6 (191.1)	165.3 (145.1)	232/1351	$W=0.0001$	<0.0001	0.57 [0.54, 0.61]
DPDD 30 days prior to BL (Number)	10.1 (7.6)	8.7 (7.5)	232/1351	$W=0.0001$	<0.05	0.43 [0.39, 0.47]
HDD 30 days prior to BL (Number)	5.0 (3.1)	3.3 (3.0)	232/1351	$W=0.0001$	<0.05	0.33 [0.29, 0.37]
PDA 30 days prior to BL (Number)	4.0 (3.0)	13.0 (12.0)	232/1351	$W=0.0001$	<0.05	0.81 [0.78, 0.84]

Significant *p*-values in **bold**. AD=Alcohol Dependence; ADS=Alcohol Dependence Scale; BL=Baseline; CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised; DrInC-2R=Drinker Inventory of Consequences-2R; DPDD=Drinks Per Drinking Day; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HDD=Heavy Drinking Days; OCDS=Obsessive Compulsive Drinking Scale; PDA=Percent Days Abstinent; *CI*=Confidence Interval; *IQR*=Interquartile Range; *P*=*P*-value; *SD*=Standard Deviation; *t*=Student's *t*-test; *W*=Wilcoxon rank-sum test; ; χ^2 =*Chi*-squared test.

Table 4.

Predictive value of sociodemographic and alcohol-related clinical characteristics differing significantly between the Brown non-treatment seekers and the COMBINE treatment seekers in relation to the COMBINE study clinical outcomes. Bolded values were statistically significant after the FDR correction.

Variable		Clinical Outcomes					
		Time to Relapse		PDA		GCO	
		Hazard Ratio [95% CI]	P	B [95% CI]	P	Odds Ratio [95% CI]	P
Sex (Male)		0.98 [0.98, 0.99]	<0.001	-0.01 [-0.13, 0.16]	0.840	0.98 [0.97, 1.00]	0.019
Race/Ethnicity (%)	African American vs. Caucasian	0.72 [0.52, 0.99]	0.024	5.22 [2.30, 12.73]	0.174	1.00 [0.57, 1.74]	0.269
	Hispanic/Latino vs. Caucasian	0.89 [0.67, 1.17]	0.331	5.55 [-0.12, 11.23]	0.055	1.16 [0.69, 1.95]	0.615
	Other vs. Caucasian	0.90 [0.59, 1.38]	0.583	21.14 [12.02, 30.25]	<0.001	2.39 [1.24, 4.62]	0.017
Education (Years)		0.98 [0.95, 1.01]	0.233	-0.17 [-0.74, 0.39]	0.544	0.92 [0.87, 0.98]	0.008
Marital Status (%)	Single vs. Married	1.27 [1.04, 1.54]	0.007	-2.17 [-5.78, 1.43]	0.238	1.59 [1.11, 2.28]	0.168
	Separated vs. Married	1.18 [0.80, 1.73]	0.343	2.66 [-4.62, 9.94]	0.473	1.99 [0.99, 3.99]	0.907
	Divorced vs. Married	1.22 [0.99, 1.51]	0.031	3.14 [-1.09, 7.36]	0.146	1.42 [0.96, 2.09]	0.050
	Widow(er) vs. Married	0.95 [0.34, 2.62]	0.912	7.35 [-9.56, 24.27]	0.394	3.91 [0.99, 15.38]	0.290
	Cohabitant vs. Married	1.56 [1.00, 2.43]	0.024	10.39 [1.35, 19.42]	0.024	4.95 [2.15, 11.38]	0.019
	Partner vs. Married	1.19 [0.66, 2.17]	0.500	2.26 [-9.00, 13.52]	0.694	1.85 [0.65, 5.25]	0.811
Employment Status (%)	Currently working full-time vs. Unemployed	1.02 [0.81, 1.27]	0.877	-0.60 [-4.85, 3.64]	0.779	0.68 [0.45, 1.02]	0.001
	Currently working part-time vs. Unemployed	1.16 [0.85, 1.58]	0.280	-0.95 [-6.81, 4.91]	0.751	1.07 [0.62, 1.86]	0.275
	Retired vs. Unemployed	1.05 [0.72, 1.53]	0.763	-1.60 [-8.56, 5.35]	0.651	0.71 [0.37, 1.37]	0.559
	Other vs. Unemployed	1.02 [0.72, 1.45]	0.899	0.64 [-5.94, 7.22]	0.848	0.99 [0.54, 1.86]	0.760
DSM-IV AD Criteria (Number)		1.10 [1.03, 1.17]	<0.001	0.08 [-1.07, 1.22]	0.897	1.18 [1.05, 1.32]	0.006
ADS (Total Score)		1.01 [1.00, 1.02]	0.022	0.33 [0.13, 0.53]	0.001	1.02 [1.00, 1.04]	0.034
OCDS (Total Score)		1.02 [1.01, 1.03]	<0.001	0.07 [-0.11, 0.25]	0.425	1.02 [1.00, 1.04]	0.035
CIWA-Ar (Total Score)		1.04 [1.00, 1.07]	0.009	-0.96 [-1.61, -0.31]	0.004	1.10 [1.04, 1.17]	0.002
BL DrInC-2R (Total Score)		1.00 [0.99, 1.01]	0.323	0.12 [0.04, 0.19]	0.001	1.01 [1.01, 1.02]	<0.001
Father with Alcohol Problems (Yes)		1.06 [0.90, 1.24]	0.430	74.73 [67.86, 81.62]	<0.001	1.09 [0.82, 1.46]	0.535

Variable	Clinical Outcomes					
	Time to Relapse		PDA		GCO	
	Hazard Ratio [95% CI]	P	B [95% CI]	P	Odds Ratio [95% CI]	P
Age of onset of AD (Years)	0.99 [0.98, 1.00]	0.093	0.02 [−0.12, 0.16]	0.782	0.98 [0.97, 0.99]	0.028
Duration of AD (Years)	0.99 [0.98, 1.00]	0.041	−0.03 [−0.19, 0.12]	0.679	0.99 [0.98, 1.01]	0.899
Total drinks 30 days prior to BL (Number)	1.01 [1.00, 1.02]	<0.001	−0.01 [−0.03, 0.01]	0.927	1.01 [1.00, 1.02]	0.001
DPDD 30 days prior to BL (Number)	1.00 [0.99, 1.01]	0.665	0.38 [0.19, 0.58]	<0.001	1.02 [0.99, 1.03]	0.086
HDD 30 days prior to BL (Number)	1.30 [1.20, 1.40]	<0.001	−2.41 [−3.59, −1.23]	<0.001	1.32 [1.17, 1.50]	<0.001

Significant *p*-values in **bold**. Other Race/Ethnicity=American Indian/Alaskan Native, Asian American/Pacific Islander, Bi- or Multi-Racial; Other Employment Status=Homemaker, Disabled; ADS=Alcohol Dependence Scale; BL=Baseline; CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised; DrInC-2R=Drinker Inventory of Consequences-2R; DPDD=Drinks Per Drinking Day; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GCO=good clinical outcome; HDD=Heavy Drinking Days; OCDS=Obsessive Compulsive Drinking Scale; PDA=percent days abstinent; *B*=regression coefficient; *CI*=Confidence Interval; *FDR*= Benjamini-Hochberg false discovery rate; *P*=*P*-value.

Table 5.

Comparison between non-treatment seekers (NTS) and treatment seekers (TS) from this study and from the studies by Ray and colleagues (2017), Rohn and colleagues (2017), and Lee and colleagues (2019).

Variable	This study	Effect Size [95% CI]	Ray et al. (2017)	Effect Size [95% CI]	Rohn et al. (2017)	Effect Size [95% CI]	Lee et al. (2019)	Effect Size [95% CI]
Sex (Male)	NTS = TS	-0.03 [-0.01, -0.05]	NTS > TS	0.05 [0.00, 0.10]	NTS > TS	0.08 [0.01, 0.15]	NTS > TS	0.08 [0.00, 0.27]
Age (Years)	NTS = TS	0.54 [0.52, 0.56]	NTS < TS	1.18 [1.03, 1.33]	NTS = TS	0.07 [-0.09, 0.24]	NTS = TS	0.65 [0.55, 0.75]
Race/Ethnicity (%)	Caucasian	0.26 [0.23, 0.28]	NTS < TS	0.31 [0.26, 0.36]	NTS < TS	0.29 [0.23, 0.36]	NTS < TS	0.33 [0.24, 0.38]
	African American		NTS > TS		NTS > TS		NTS > TS	
	Hispanic/Latino		NTS > TS		NTS < TS		NTS < TS	
	Other		NTS > TS		NTS < TS		NTS = TS	
Education (Years)	NTS < TS	0.62 [0.59, 0.64]	NTS < TS	0.18 [0.03, 0.33]	NTS = TS	0.11 [-0.06, 0.27]	NTS = TS	0.46 [0.37, 0.56]
Marital Status (%)	Single	0.31 [0.29, 0.34]	NTS > TS	0.57 [0.42, 0.72]	N/A	N/A	N/A	N/A
	Married		NTS < TS		N/A	N/A	N/A	N/A
	Separated		NTS < TS		N/A	N/A	N/A	N/A
	Divorced		NTS < TS		N/A	N/A	N/A	N/A
	Widow(er)		NTS < TS		N/A	N/A	N/A	N/A
	Cohabitant		NTS < TS		N/A	N/A	N/A	N/A
	Partner		NTS < TS		N/A	N/A	N/A	N/A
Employment Status (%)	Currently working full-time	0.33 [0.30, 0.35]	NTS > TS	N/A	N/A	N/A	N/A	N/A
	Currently working part-time		NTS = TS		N/A	N/A	N/A	N/A
	Retired		NTS = TS		N/A	N/A	N/A	N/A
	Unemployed		NTS > TS		N/A	N/A	N/A	N/A
	Other		NTS = TS		N/A	N/A	N/A	N/A
SBP (mmHg)	NTS = TS	0.77 [0.72, 0.81]	N/A	N/A	N/A	N/A	N/A	N/A
DBP (mmHg)	NTS = TS	0.74 [0.69, 0.87]	N/A	N/A	N/A	N/A	N/A	N/A

Variable	This study	Effect Size [95% CI]	Ray et al. (2017)	Effect Size [95% CI]	Rohn et al. (2017)	Effect Size [95% CI]	Lee et al. (2019)	Effect Size [95% CI]
BMI (Kg/m ²)	N/A	N/A	N/A	N/A	N/A	N/A	NTS > TS	0.50 [0.39, 0.61]
ALT (U/l)	N/A	N/A	N/A	N/A	NTS < TS	0.50 [0.33, 0.67]	NTS < TS	0.63 [0.52, 0.72]
AST (U/l)	N/A	N/A	N/A	N/A	NTS < TS	0.50 [0.34, 0.67]	NTS < TS	0.65 [0.55, 0.75]
GGT (U/l)	N/A	N/A	N/A	N/A	NTS < TS	0.39 [0.23, 0.56]	NTS < TS	0.69 [0.56, 0.75]
Serum Iron (µg)	N/A	N/A	N/A	N/A	N/A	N/A	NTS < TS	0.54 [0.43, 0.64]
DSM-IV AD Criteria (Number)	NTS < TS	0.85 [0.83, 0.87]	NTS < TS	0.95 [0.80, 1.10]	NTS < TS	1.78 [1.59, 1.97]	NTS < TS	0.65 [0.54, 0.76]
DSM-IV Alcohol Abuse Criteria (Number)	N/A	N/A	N/A	N/A	N/A	N/A	NTS < TS	0.61 [0.50, 0.71]
DSM-IV AD Criterion "Drinking despite psychological problems" (Yes)	N/A	N/A	N/A	N/A	N/A	N/A	NTS < TS	0.37 [0.18, 0.57]
DSM-IV Substance Dependence Diagnosis (Yes)	N/A	N/A	N/A	N/A	N/A	N/A	NTS < TS	0.25 [0.13, 0.36]
ADS (Total Score)	NTS < TS	0.83 [0.80, 0.86]	NTS < TS	0.57 [0.42, 0.72]	N/A	N/A	N/A	N/A
OCDs (Total Score)	NTS < TS	0.86 [0.83, 0.88]	NTS < TS	0.70 [0.55, 0.85]	N/A	N/A	N/A	N/A
CIWA-Ar (Total Score)	NTS < TS	0.68 [0.65, 0.71]	NTS = TS	0.59 [0.44, 0.74]	N/A	N/A	N/A	N/A
Baseline DrInC-2R (Total Score)	NTS < TS	0.87 [0.84, 0.90]	NTS < TS	0.67 [0.52, 0.82]	N/A	N/A	N/A	N/A
Father with Alcohol Problems (Yes)	NTS < TS	0.11 [0.09, 0.13]	N/A	N/A	NTS < TS	0.14 [0.01, 0.42]	NTS < TS	0.08 [0.00, 0.25]
Mother with Alcohol Problems (Yes)	NTS = TS	-0.04 [-0.02, -0.06]	N/A	N/A	NTS < TS	0.12 [0.03, 0.39]	NTS < TS	0.06 [0.00, 0.25]
Age of onset of AD (Years)	NTS < TS	0.75 [0.71, 0.78]	N/A	N/A	N/A	N/A	N/A	N/A
Duration of AD (Years)	NTS > TS	0.55 [0.51, 0.59]	NTS < TS	0.55 [0.40, 0.70]	N/A	N/A	N/A	N/A
Total drinks 30 days prior to BL (Number)	NTS > TS	0.57 [0.54, 0.61]	NTS < TS	0.18 [0.03, 0.32]	NTS < TS	0.64 [0.47, 0.82]	NTS < TS	0.64 [0.54, 0.73]
DPDD 30 days prior to BL (Number)	NTS > TS	0.43 [0.39, 0.47]	NTS < TS	0.27 [0.13, 0.42]	NTS < TS	0.74 [0.57, 0.92]	NTS < TS	0.64 [0.53, 0.75]

Variable	This study	Effect Size [95% CI]	Ray et al. (2017)	Effect Size [95% CI]	Rohn et al. (2017)	Effect Size [95% CI]	Lee et al. (2019)	Effect Size [95% CI]
HDD 30 days prior to BL (Number)	NTS > TS	0.33 [0.29, 0.37]	N/A	N/A	NTS < TS	0.58 [0.41, 0.75]	NTS < TS	0.44 [0.34, 0.54]
PDA 30 days prior to BL (Number)	NTS < TS	0.81 [0.78, 0.84]	N/A	N/A	N/A	N/A	NTS = TS	0.59 [0.49, 0.69]
CPRS Depression (Score)	N/A	N/A	N/A	N/A	NTS > TS	1.16 [0.98, 1.33]	NTS < TS	0.86 [0.79, 0.92]
CPRS Anxiety (Score)	N/A	N/A	N/A	N/A	NTS > TS	0.89 [0.71, 1.06]	NTS < TS	0.84 [0.77, 0.90]
WASI IQ (Total Score)	N/A	0.55 [0.51, 0.59]	N/A	N/A	NTS < TS	0.33 [0.17, 0.50]	NTS = TS	0.39 [0.29, 0.50]
NEO PI-R Neuroticism (Score)	N/A	N/A	N/A	N/A	NTS < TS	0.60 [0.43, 0.77]	NTS < TS	0.50 [0.39, 0.61]
NEO PI-R Extraversion (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.09 [-0.07, 0.26]	NTS > TS	0.25 [0.17, 0.34]
NEO PI-R Openness (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.06 [-0.11, 0.22]	NTS = TS	0.34 [0.24, 0.45]
NEO PI-R Conscientiousness (Score)	N/A	N/A	N/A	N/A	NTS > TS	0.35 [0.18, 0.52]	NTS > TS	0.26 [0.16, 0.36]
NEO PI-R Agreeableness (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.03 [-0.13, 0.20]	NTS = TS	0.36 [0.25, 0.48]
BIS Attentional Impulsivity (Score)	N/A	N/A	N/A	N/A	NTS < TS	0.47 [0.30, 0.64]	NTS < TS	0.56 [0.45, 0.66]
BIS Motor Impulsivity (Score)	N/A	N/A	N/A	N/A	NTS < TS	0.33 [0.16, 0.50]	NTS = TS	0.45 [0.34, 0.56]
BIS Non-Planning Impulsivity (Score)	N/A	N/A	N/A	N/A	NTS < TS	0.48 [0.31, 0.65]	NTS < TS	0.61 [0.51, 0.72]
UPPS-P Negative Urgency (Score)	N/A	N/A	N/A	N/A	NTS < TS	0.77 [0.60, 0.94]	NTS = TS	0.56 [0.46, 0.67]
UPPS-P Positive Urgency (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.26 [0.08, 0.42]	NTS = TS	0.50 [0.41, 0.60]
UPPS-P Premeditation (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.17 [0.00, 0.34]	NTS = TS	0.52 [0.42, 0.67]
UPPS-P Perseverance (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.17 [-0.00, 0.33]	NTS < TS	0.62 [0.51, 0.73]
UPPS-P Sensation Seeking (Score)	N/A	N/A	N/A	N/A	NTS = TS	0 [-0.17, -0.17]	NTS = TS	0.42 [0.31, 0.52]
BPAQ (Total Score)	N/A	N/A	N/A	N/A	NTS = TS	0.10 [-0.07, 0.27]	NTS = TS	0.50 [0.35, 0.57]

Variable	This study	Effect Size [95% CI]	Ray et al. (2017)	Effect Size [95% CI]	Rohn et al. (2017)	Effect Size [95% CI]	Lee et al. (2019)	Effect Size [95% CI]
CTQ Emotional Abuse (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.27 [0.11, 0.44]	NTS = TS	0.48 [0.38, 0.57]
CTQ Physical Abuse (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.12 [-0.05, 0.28]	NTS = TS	0.40 [0.29, 0.50]
CTQ Sexual Abuse (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.22 [0.05, 0.38]	NTS = TS	0.52 [0.44, 0.59]
CTQ Emotional Neglect (Score)	N/A	N/A	N/A	N/A	NTS = TS	0.06 [-0.11, 0.22]	NTS = TS	0.43 [0.34, 0.54]
CTQ Physical Neglect (Score)	N/A	N/A	N/A	N/A	NTS > TS	0.08 [-0.08, 0.25]	NTS = TS	0.39 [0.29, 0.49]
ELSQ (Total Score)	N/A	N/A	N/A	N/A	NTS < TS	0.38 [0.21, 0.55]	NTS = TS	0.49 [0.39, 0.60]

Comparable findings from this study and any of the three other studies in **bold**. NTS=Non-Treatment Seekers; TS=Treatment seekers; DBP=Diastolic Blood Pressure; SBP=Systemic Blood Pressure; Other Race/Ethnicity=American Indian/Alaskan Native, Asian American/Pacific Islander, Bi- or Multi-Racial; Other Employment Status=Homemaker, Disabled; BMI=Body Mass Index; ADS=Alcohol Dependence Scale; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; BIS=Barratt Impulsiveness Scale; BL=Baseline; BPAQ=Buss-Perry Aggression Questionnaire; CPRS=Comprehensive Psychopathological Rating Scale; CIWA-Ar=Clinical Institute Withdrawal Assessment of Alcohol Scale-Revised; CTQ=Childhood Trauma Questionnaire; DrInC-2R=Drinker Inventory of Consequences-2R; DPDD=Drinks Per Drinking Day; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ; ELSQ=Early Life Stress Questionnaire; GGT=Gamma-Glutamyl Transpeptidase; HDD=Heavy Drinking Days; IQ=Intelligence Quotient; NEO PI-R=Neuroticism-Extraversion-Openness Personality Inventory-Revised; PDA=Percent Days Abstinent; UPPS-P=Urgency, Premeditation (Lack of), Perseverance (Lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; WASI=Wechsler Abbreviated Scale of Intelligence; CI=Confidence Interval; N/A=not applicable.